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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6:

G01N 33/53

A2

(11) International Publication Number: WO 98/45704

(43) International Publication Date: 15 October 1998 (15.10.98)

(21) International Application Number:

PCT/DK98/00145

(22) International Filing Date:

7 April 1998 (07.04.98)

(30) Priority Data:

0392/97

7 April 1997 (07.04.97)

DK

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: A METHOD FOR EXTRACTING QUANTITATIVE INFORMATION RELATING TO AN INFLUENCE ON A CELLULAR RESPONSE

(57) Abstract

Cells are genetically modified to expresss a luminophore, e.g., a modified (F64L, S65T, Y66H) Green Fluorescent Protein (GFP, EGFP) coupled to a component of an intracellular signalling pathway such as a transcription factor, a cGMP- or cAMP-dependent protein kinase, a cyclin-, calmodulin- or phospholipid-dependent or mitogen-activated serine/threonin protein kinase, a tyrosine protein kinase, or a protein phosphatase (e.g. PKA, PKC, Erk, Smad, VASP, actin, p38, Jnk1, PKG, IkappaB, CDK2, Grk5, Zap70, p85, protein-tyrosine phosphatase 1C, Stat5, NFAT, NFkappaB, RhoA, PKB). An influence modulates the intracellular signalling pathway in such a way that the luminophore is being redistributed or translocated with the component in living cells in a manner experimentally determined to be correlated to the degree of the influence. Measurement of redistribution is performed by recording of light intensity, fluorescence lifetime, polarization, wavelength shift, resonance energy transfer, or other properties by an apparatus consisting of e.g. a fluorescence microscope and a CCD camera. Data stored as digital images are processed to numbers representing the degree of redistribution. The method can be used as a screening program for identifying a compound that modulates a component and is capable of treating a disease related to the function of the component.

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A METHOD for extracting quantitative information relating to an influence on a cellular response

FIELD OF INVENTION

5 The present invention relates to a method and tools for extracting quantitative information relating to an influence, on a cellular response, in particular an influence caused by contacting or incubating the cell with a substance influencing a cellular response, where the cellular response is manifested in redistribution of at least one component in the cell. In particular, the invention relates to a method for extracting quantitative information relating to an influen-10 ce on an intracellular pathway involving redistribution of at least one component associated with the pathway. The method of the invention may be used as a very efficient procedure for testing or discovering the influence of a substance on a physiological process, for example in connection with screening for new drugs, testing of substances for toxicity, identifying drug targets for known or novel drugs. Other valuable uses of the method and technology of the 15 invention will be apparent to the skilled person on the basis of the following disclosure. In a particular embodiment of the invention, the present invention relates to a method of detecting intracellular translocation or redistribution of biologically active polypeptides, preferably an enzyme, affecting intracellular processes, and a DNA construct and a cell for use in the

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method.

BACKGROUND OF THE INVENTION

Intracellular pathways are tightly regulated by a cascade of components that undergo modulation in a temporally and spatially characteristic manner. Several disease states can be attributed to altered activity of individual signalling components (i.e. protein kinases, protein phosphatases, transcription factors). These components therefore render themselves as attractive targets for therapeutic intervention.

Protein kinases and phosphatases are well described components of several intracellular signalling pathways. The catalytic activity of protein kinases and phosphatases are assumed to play a role in virtually all regulatable cellular processes. Although the involvement of protein kinases in cellular signalling and regulation have been subjected to extensive studies, detailed knowledge on e.g. the exact timing and spatial characteristics of signalling events is often difficult to obtain due to lack of a convenient technology.

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Novel ways of monitoring specific modulation of intracellular pathways in intact, living cells is assumed to provide new opportunities in drug discovery, functional genomics, toxicology, patient monitoring etc.

The spatial orchestration of protein kinase activity is likely to be essential for the high degree of specificity of individual protein kinases. The phosphorylation mediated by protein kinases is balanced by phosphatase activity. Also within the family of phosphatases translocation has been observed, e.g. translocation of PTP2C to membrane ruffles [(Cossette *et al.*1996)], and likewise is likely to be indicative of phosphatase activity.

Protein kinases often show a specific intracellular distribution before, during and after activation. Monitoring the translocation processes and/or redistribution of individual protein kinases or subunits thereof is thus likely to be indicative of their functional activity. A connection between translocation and catalytic activation has been shown for protein kinases like the diacyl glycerol (DAG)-dependent protein kinase C (PKC), the cAMP-dependent protein kinase (PKA) [(DeBernardi et al.1996)] and the mitogen-activated-protein kinase Erk-1 [(Sano et al.1995)].

Commonly used methods of detection of intracellular localisation/activity of protein kinases and phosphatases are immunoprecipitation, Western blotting and immunocytochemical detection.

Taking the family of diacyl glycerol (DAG)-dependent protein kinase Cs (PKCs) as an example, it has been shown that individual PKC isoforms that are distributed among different tissues and cells have different activator requirements and undergo differential translocation in response to activation. Catalytically inactive DAG-dependent PKCs are generally distributed throughout the cytoplasm, whereas they upon activation translocate to become associated with different cellular components, e.g. plasma membrane [(Farese, 1992),(Fulop Jr. et al.1995)] nucleus [(Khalil et al.1992)], cytoskeleton [(Blobe et al.1996)]. The translocation phenomenon being indicative of PKC activation has been monitored using different approaches: a) immunocytochemistry where the localisation of individual isoforms can be detected after permeabilisation and fixation of the cells [(Khalil et al.1992)]; and b) tagging all DAG-dependent PKC isoforms with a fluorescently labelled phorbol myristate acetate (PMA) [(Godson et al.1996)]; and c) chemical tagging PKC b1 with the fluorophore Cy3 [(Bastiaens & Jovin 1996)] and d) genetic tagging of PKCα ([Schmidt et al. 1997]) and of PKCγ and PKC ε ([Sakai et al. 1996]). The first method does not provide dynamic information whereas the latter methods will. Tagging PKC with fluorescently labelled phorbol myristate acetate cannot

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distinguish between different DAG-dependent isoforms of PKC but will label and show movement of all isoforms. Chemical and genetic labelling of specific DAG-dependent PKCs confirmed that they in an isoform specific manner upon activation move to cell periphery or nucleus.

In an alternative method, protein kinase A activity has been measured in living cells by chemical labelling one of the kinase's subunit (Adams *et al.*1991). The basis of the methodology is that the regulatory and catalytic subunit of purified protein kinase A is labelled with fluorescein and rhodamine, respectively. At low cAMP levels protein kinase A is assembled in a heterotetrameric form which enables fluorescence resonance energy transfer between the two fluorescent dyes. Activation of protein kinase A leads to dissociation of the complex, thereby eliminating the energy transfer. A disadvantage of this technology is that the labelled protein kinase A has to be microinjected into the cells of interest. This highly invasive technique is cumbersome and not applicable to large scale screening of biologically active substances. A further disadvantage of this technique as compared to the presented invention is that the labelled protein kinase A cannot be inserted into organisms/animals as a transgene.

Recently it was discovered that Green Fluorescent Protein (GFP) expressed in many different cell types, including mammalian cells, became highly fluorescent [(Chalfie et al. 1994)]. WO95/07463 describes a cell capable of expressing GFP and a method for detecting a protein of interest in a cell based on introducing into a cell a DNA molecule having DNA sequence encoding the protein of interest linked to DNA sequence encoding a GFP such that the protein produced by the DNA molecule will have the protein of interest fused to the GFP, then culturing the cells in conditions permitting expression of the fused protein and detecting the location of the fluorescence in the cell, thereby localizing the protein of interest in the cell. However, examples of such fused proteins are not provided, and the use of fusion proteins with GFP for detection or quantitation of translocation or redistribution of biologically active polypeptides affecting intracellular processes upon activation, such as proteins involved in signalling pathways, e.g. protein kinases or phosphatases, has not been suggested. WO 95/07463 further describes cells useful for the detection of molecules, such as hormones or heavy metals, in a biological sample, by operatively linking a regulatory element of the gene which is affected by the molecule of interest to a GFP, the presence of the molecules will affect the regulatory element which in turn will affect the expression of the GFP. In this way the gene encoding GFP is used as a reporter gene in a cell which is constructed for monitoring the presence of a specific molecular identity.

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Green Fluorescent Protein has been used in an assay for the detection of translocation of the glucocorticoid receptor (GR) [Carey, KL et al., The Journal of Cell Biology, Vol. 133, No. 5, p. 985-996 (1996)]. A GR-S65TGFP fusion has been used to study the mechanisms involved in translocation of the glucocorticoid receptor (GR) in response to the agonist dexamethasone from the cytosol, where it is present in the absence of a ligand, through the nuclear pore to the nucleus where it remains after ligand binding. The use of a GR-GFP fusion enables real-time imaging and quantitation of nuclear/cytoplasmic ratios of the fluorescence signal.

Many currently used screening programmes designed to find compounds that affect protein kinase activity are based on measurements of kinase phosphorylation of artificial or natural substrates, receptor binding and/or reporter gene expression.

DISCLOSURE OF THE INVENTION

The present invention provides an important new dimension in the investigation of cellular systems involving redistribution in that the invention provides quantification of the redistribution responses or events caused by an influence, typically contact with a chemical substance or mixture of chemical substances, but also changes in the physical environment. The quantification makes it possible to set up meaningful relationships, expressed numerically, or as curves or graphs, between the influences (or the degree of influences) on cellular systems and the redistribution response. This is highly advantageous because, as has been found, the quantification can be achieved in both a fast and reproducible manner, and - what is perhaps even more important - the systems which become quantifiable utilizing the method of the invention are systems from which enormous amounts of new information and insight can be derived.

The present screening assays have the distinct advantage over other screening assays, e.g., receptor binding assays, enzymatic assays, and reporter gene assays, in providing a system in which biologically active substances with completely novel modes of action, e.g. inhibition or promotion of redistribution/translocation of a biologically active polypeptide as a way of regulating its action rather than inhibition/activation of enzymatic activity, can be identified in a way that insures very high selectivity to the particular isoform of the biologically active polypeptide and further development of compound selectivity versus other isoforms of

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the same biologically active polypeptide or other components of the same signalling pathway.

In its broadest aspect, the invention relates to a method for extracting quantitative information relating to an influence on a cellular response, the method comprising recording variation, caused by the influence on a mechanically intact living cell or mechanically intact living cells, in spatially distributed light emitted from a luminophore, the luminophore being present in the cell or cells and being capable of being redistributed in a manner which is related with the degree of the influence, and/or of being modulated by a component which is capable of being redistributed in a manner which is related to the degree of the influence, the association resulting in a modulation of the luminescence characteristics of the luminophore, detecting and recording the spatially distributed light from the luminophore, and processing the recorded variation in the spatially distributed light to provide quantitative information correlating the spatial distribution or change in the spatial distribution to the degree of the influence. In a preferred embodiment of the invention the luminophore, which is present in the cell or cells, is capable of being redistributed by modulation of an intracellular pathway, in a manner which is related to the redistribution of at least one component of the intracellular pathway. In another preferred embodiment of the invention, the luminophore is a fluorophore.

The cells

In the invention the cell and/or cells are mechanically intact and alive throughout the experiment. In another embodiment of the invention, the cell or cells is/are fixed at a point in time after the application of the influence at which the response has been predetermined to be significant, and the recording is made at an arbitrary later time.

The mechanically intact living cell or cells could be selected from the group consisting of fungal cell or cells, such as a yeast cell or cells; invertebrate cell or cells including insect cell or cells; and vertebrate cell or cells, such as mammalian cell or cells. This cell or these cells is/are incubated at a temperature of 30°C or above, preferably at a temperature of from 32°C to 39°C, more preferably at a temperature of from 35°C to 38°C, and most preferably at a temperature of about 37°C during the time period over which the influence is observed. In one aspect of the invention the mechanically intact living cell is part of a matrix of identical or non-identical cells.

A cell used in the present invention should contain a nucleic acid construct encoding a fusion polypeptide as defined herein and be capable of expressing the sequence encoded by the construct. The cell is a eukaryotic cell selected from the group consisting of fungal cells, such as yeast cells; invertebrate cells including insect cells; vertebrate cells such as mammalian cells. The preferred cells are mammalian cells.

In another aspect of the invention the cells could be from an organism carrying in at least one of its component cells a nucleic acid sequence encoding a fusion polypeptide as defined herein and be capable of expressing said nucleic acid sequence. The organism is selected from the group consisting of unicellular and multicellular organisms, such as a mammal.

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The luminophore

The luminophore is the component which allows the redistribution to be visualised and/or recorded by emitting light in a spatial distribution related to the degree of influence. In one embodiment of the invention, the luminophore is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence. In another embodiment, the luminophore is capable of associating with a component which is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence. In another embodiment, the luminophore correlation between the redistribution of the luminophore and the degree of the influence could be determined experimentally. In a preferred aspect of the invention, the luminophore is capable of being redistributed in substantially the same manner as the at least one component of an intracellular pathway. In yet another embodiment of the invention, the luminophore is capable of being quenched upon spatial association with a component which is redistributed by modulation of the pathway, the quenching being measured as a change in the intensity of the luminescence.

The luminophore could be a fluorophore. In a preferred embodiment of the invention, the luminophore could be a polypeptide encoded by and expressed from a nucleotide sequence harboured in the cell or cells. The luminophore could be a hybrid polypeptide comprising a fusion of at least a portion of each of two polypeptides one of which comprises a luminescent polypeptide and the other one of which comprises a biologically active polypeptide, as defined herein.

The luminescent polypeptide could be a GFP as defined herein or could be selected from the group consisting of green fluorescent proteins having the F64L mutation as defined herein

such as F64L-GFP, F64L-Y66H-GFP, F64L-S65T-GFP, and EGFP. The GFP could be N- or C-terminally tagged, optionally via a peptide linker, to the biologically active polypeptide or a part or a subunit thereof. The fluorescent probe could be a component of a intracellular signalling pathway. The probe is coded for by a nucleic acid construct.

The pathway of investigation in the present invention could be an intracellular signalling pathway.

The influence

In a preferred embodiment of the invention, the influence could be contact between the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance and/or incubation of the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance. The influence will modulate the intracellular processes. In one aspect the modulation could be an activation of the intracellular processes. In another aspect the modulation could be an deactivation of the intracellular processes. In yet another aspect, the influence could inhibit or promote the redistribution without directly affecting the metabolic activity of the component of the intracellular processes.

In one embodiment the invention is used as a basis for a screening program, where the effect of unknown influences such as a compound library, can be compared to influence of known reference compounds under standardised conditions.

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The recording

In addition to the intensity, there are several parameters of fluorescence or luminescence which can be modulated by the effect of the influence on the underlying cellular phenomena, and can therefore be used in the invention. Some examples are resonance energy transfer, fluorescence lifetime, polarisation, wavelength shift. Each of these methods requires a particular kind of filter in the emission light path to select the component of the light desired and reject other components. The recording of property of light could be in the form of an ordered array of values such as a CCD array or a vacuum tube device such as a vidicon tube.

In one embodiment of the invention, the spatially distributed light emitted by a luminophore could be detected by a change in the resonance energy transfer between the luminophore and another luminescent entity capable of delivering energy to the luminophore, each of

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which has been selected or engineered to become part of, bound to or associated with particular components of the intracellular pathway. In this embodiment, either the luminophore or the luminescent entity capable of delivering energy to the luminophore undergoes redistribution in response to an influence. The resonance energy transfer would be measured as a change in the intensity of emission from the luminophore, preferably sensed by a single channel photodetector which responds only to the average intensity of the luminophore in a non-spatially resolved fashion.

In one embodiment of the invention, the recording of the spatially distributed light could be made at a single point in time after the application of the influence. In another embodiment, the recording could be made at two points in time, one point being before, and the other point being after the application of the influence. The result or variation is determined from the change in fluorescence compared to the fluorescence measured prior to the influence or modulation. In another embodiment of the invention, the recording could be performed at a series of points in time, in which the application of the influence occurs at some time after the first time point in the series of recordings, the recording being performed, e.g., with a predetermined time spacing of from 0.1 seconds to 1 hour, preferably from 1 to 60 seconds, more preferably from 1 to 30 seconds, in particular from 1 to 10 seconds, over a time span of from 1 second to 12 hours, such as from 10 seconds to 12 hours, e.g., from 10 seconds to one hour, such as from 60 seconds to 30 minutes or 20 minutes. The result or variation is determined from the change in fluorescence over time. The result or variation could also be determined as a change in the spatial distribution of the fluorescence over time.

Apparatus

The recording of spatially distributed luminescence emitted from the luminophore is performed by an apparatus for measuring the distribution of fluorescence in the cell or cells, and thereby any change in the distribution of fluorescence in the cell or cells, which includes at a minimum the following component parts: (a) a light source, (b) a method for selecting the wavelength(s) of light from the source which will excite the fluorescence of the protein, (c) a device which can rapidly block or pass the excitation light into the rest of the system, (d) a series of optical elements for conveying the excitation light to the specimen, collecting the emitted fluorescence in a spatially resolved fashion, and forming an image from this fluorescence emission, (e) a bench or stand which holds the container of the cells being measured in a predetermined geometry with respect to the series of optical elements, (f) a detector to

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record the spatially resolved fluorescence in the form of an image, (g) a computer or electronic system and associated software to acquire and store the recorded images, and to compute the degree of redistribution from the recorded images.

In a preferred embodiment of the invention the apparatus system is automated. In one embodiment the components in d and e mentioned above comprise a fluorescence microscope. In one embodiment the component in f mentioned above is a CCD camera.

In one embodiment the image is formed and recorded by an optical scanning system.

In one embodiment a liquid addition system is used to add a known or unknown compound to any or all of the cells in the cell holder at a time determined in advance. Preferably, the liquid addition system is under the control of the computer or electronic system. Such an automated system can be used for a screening program due to its ability to generate results from a larger number of test compounds than a human operator could generate using the apparatus in a manual fashion.

15 Quantitation of the influence

The recording of the variation or result with respect to light emitted from the luminophore is performed by recording the spatially distributed light as one or more digital images, and the processing of the recorded variation to reduce it to one or more numbers representative of the degree of redistribution comprises a digital image processing procedure or combination of digital image processing procedures. The quantitative information which is indicative of the degree of the cellular response to the influence or the result of the influence on the intracellular pathway is extracted from the recording or recordings according to a predetermined calibration based on responses or results, recorded in the same manner, to known degrees of a relevant specific influence. This calibration procedure is developed according to principles described below (Developing an Image-based Assay Technique). Specific descriptions of the procedures for particular assays are given in the examples.

While the stepwise procedure necessary to reduce the image or images to the value representative of the is particular to each assay, the individual steps are generally well-known methods of image processing. Some examples of the individual steps are point operations such as subtraction, ratioing, and thresholding, digital filtering methods such as smoothing, sharpening, and edge detection, spatial frequency methods such as Fourier filtering, image cross-correlation and image autocorrelation, object finding and classification (blob analysis),

and colour space manipulations for visualisation. In addition to the algorithmic procedures, heuristic methods such as neural networks may also be used.

Nucleic acid constructs

- The nucleic acid constructs used in the present invention encode in their nucleic acid sequences fusion polypeptides comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and a GFP, preferably an F64L mutant of GFP, N- or C-terminally fused, optionally via a peptide linker, to the biologically active polypeptide or part thereof.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein kinase or a phosphatase.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a transcription factor or a part thereof which changes cellular localisation upon activation.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein, or a part thereof, which is associated with the cytoskeletal network and which changes cellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein kinase or a part thereof which changes cellular localisation upon activation.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a tyrosine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a phospholipid-dependent serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cAMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation. In a preferred embodiment the biologically active polypeptide encoded by the nucleic acid construct is a PKAc-F64L-S65T-GFP fusion.

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In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cGMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a calmodulin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a mitogen-activated serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation. In preferred embodiments the biologically active polypeptide encoded by the nucleic acid constructs are an ERK1-F64L-S65T-GFP fusion or an EGFP-ERK1 fusion.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cyclin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein phosphatase or a part thereof capable of changing cellular localisation upon activation.

In one preferred embodiment of the invention the nucleic acid constructs may be DNA constructs.

- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct In one embodiment the gene encoding GFP in the nucleic acid construct is derived from Aequorea victoria. In a preferred embodiment the gene encoding GFP in the nucleic acid construct is EGFP or a GFP variant selected from F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP.
- In preferred embodiments of the invention the DNA constructs which can be identified by any of the DNA sequences shown in SEQ ID NO: 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142 or are variants of these sequences capable of encoding the same fusion polypeptide or a fusion polypeptide which is biologically equivalent thereto, e.g. an isoform, or a splice variant or a homologue from another species.

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Screening program

The present invention describes a method that may be used to establish a screening program for the identification of biologically active substances that directly or indirectly affects intracellular signalling pathways and because of this property are potentially useful as medicaments. Based on measurements in living cells of the redistribution of spatially resolved luminescence from luminophores which undergo a change in distribution upon activation or deactivation of an intracellular signalling pathway the result of the individual measurement of each substance being screened indicates its potential biological activity.

In one embodiment of the invention the screening program is used for the identification of a biologically toxic substance as defined herein that exerts its toxic effect by interfering with an intracellular signalling pathway. Based on measurements in living cells of the redistribution of spatially resolved luminescence from luminophores which undergo a change in distribution upon activation or deactivation of an intracellular signalling pathway the result of the individual measurement of each substance being screened indicates its potential biologically toxic activity. In one embodiment of a screening program a compound that modulates a component of an intracellular pathway as defined herein, can be found and the therapeutic amount of the compound estimated by a method according to the method of the invention. In a preferred embodiment the present invention leads to the discovery of a new way of treating a condition or disease related to the intracellular function of a biologically active polypeptide comprising administration to a patient suffering from said condition or disease of an effective amount of a compound which has been discovered by any method according to the invention. In another preferred embodiment of the invention a method is established for identification of a new drug target or several new drug targets among the group of biologically active polypeptides which are components of intracellular signalling pathways.

In another embodiment of the invention an individual treatment regimen is established for the selective treatment of a selected patient suffering from an ailment where the available medicaments used for treatment of the ailment are tested on a relevant primary cell or cells obtained from said patient from one or several tissues, using a method comprising transfecting the cell or cells with at least one DNA sequence encoding a fluorescent probe according to the invention, transferring the transfected cell or cells back the said patient, or culturing the cell or cells under conditions permitting the expression of said probes and exposing it to an array of the available medicaments, then comparing changes in fluorescence patterns or redistribution patterns of the fluorescent probes in the intact living cell or cells to

detect the cellular response to the specific medicaments (obtaining a cellular action profile), then selecting one or more medicament or medicaments based on the desired activity and acceptable level of side effects and administering an effective amount of these medicaments to the selected patient.

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Back-tracking of a signal transduction pathway

The present invention describes a method that may be used to establish a screening program for back-tracking signal transduction pathways as defined herein. In one embodiment the screening program is used to establish more precisely at which level one or several compounds affect a specific signal transduction pathway by successively or in parallel testing the influence of the compound or compounds on the redistribution of spatially resolved luminescence from several of the luminophores which undergo a change in distribution upon activation or deactivation of the intracellular signalling pathway under study.

15 Construction and testing of probes

In general, a probe, i.e. a "GeneX"-GFP fusion or a GFP-"GeneX" fusion, is constructed using PCR with "GeneX"-specific primers followed by a cloning step to fuse "GeneX" in frame with GFP. The fusion may contain a short vector derived sequence between "GeneX" and GFP (e.g. part of a multiple cloning site region in the plasmid) resulting in a peptide linker between "GeneX" and GFP in the resulting fusion protein.

Detailed stepwise procedure:

- Identifying the sequence of the gene. This is most readily done by searching a depository of genetic information, e.g. the GenBank Sequence Database, which is widely available and routinely used by molecular biologists. In the specific examples below the GenBank Accession number of the gene in question is provided.
- Design of gene-specific primers. Inspection of the sequence of the gene allows design of gene-specific primers to be used in a PCR reaction. Typically, the top-strand primer encompasses the ATG start codon of the gene and the following ca. 20 nucleotides, while the bottom-strand primer encompasses the stop codon and the ca. 20 preceding nucleotides, if

the gene is to be fused behind GFP, i.e. a GFP-"GeneX" fusion. If the gene is to be fused in front of GFP, i.e. a "GeneX"-GFP fusion, a stop codon must be avoided. Optionally, the full length sequence of GeneX may not be used in the fusion, but merely the part which localizes and redistributes like GeneX in response to a signal.

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In addition to gene-specific sequences, the primers contain at least one recognition sequence for a restriction enzyme, to allow subsequent cloning of the PCR product. The sites are chosen so that they are unique in the PCR product and compatible with sites in the cloning vector. Furthermore, it may be necessary to include an exact number of nucleotides between the restriction enzyme site and the gene-specific sequence in order to establish the correct reading frame of the fusion gene and/or a translation initiation consensus sequence. Lastly, the primers always contain a few nucleotides in front of the restriction enzyme site to allow efficient digestion with the enzyme.

- -Identifying a source of the gene to be amplified. In order for a PCR reaction to produce a product with gene-specific primers, the gene-sequence must initially be present in the reaction, e.g. in the form of cDNA. Information in GenBank or the scientific literature will usually indicate in which tissue(s) the gene is expressed, and cDNA libraries from a great variety of tissues or cell types from various species are commercially available, e.g. from Clontech
 (Palo Alto), Stratagene (La Jolla) and Invitrogen (San Diego). Many genes are also available in cloned form from The American Type Tissue Collection (Virginia).
 - Optimizing the PCR reaction. Several factors are known to influence the efficiency and specificity of a PCR reaction, including the annealing temperature of the primers, the concentration of ions, notably Mg²+ and K⁺, present in the reaction, as well as pH of the reaction. If the result of a PCR reaction is deemed unsatisfactory, it might be because the parameters mentioned above are not optimal. Various annealing temperatures should be tested, e.g. in a PCR machine with a built-in temperature gradient, available from e.g. Stratagene (La Jolla), and/or various buffer compositions should be tried, e.g. the OptiPrime buffer system from Stratagene (La Jolla).

- Cloning the PCR product. The vector into which the amplified gene product will be cloned and fused with GFP will already have been taken into consideration when the primers were designed. When choosing a vector, one should at least consider in which cell types the probe subsequently will be expressed, so that the promoter controlling expression of the probe is compatible with the cells. Most expression vectors also contain one or more selective markers, e.g. conferring resistance to a drug, which is a useful feature when one wants to make stable transfectants. The selective marker should also be compatible with the cells to be used.

The actual cloning of the PCR product should present no difficulty as it typically will be a one-step cloning of a fragment digested with two different restriction enzymes into a vector digested with the same two enzymes. If the cloning proves to be problematic, it may be because the restriction enzymes did not work well with the PCR fragment. In this case one could add longer extensions to the end of the primers to overcome a possible difficulty of digestion close to a fragment end, or one could introduce an intermediate cloning step not based on restriction enzyme digestion. Several companies offer systems for this approach, e.g. Invitrogen (San Diego) and Clontech (Palo Alto).

Once the gene has been cloned and, in the process, fused with the GFP gene, the resulting product, usually a plasmid, should be carefully checked to make sure it is as expected. The most exact test would be to obtain the nucleotide sequence of the fusion-gene.

Testing the probe

Once a DNA construct for a probe has been generated, its functionality and usefulness may be tested by subjecting it to the following tests:

- Transfecting it into cells capable of expressing the probe. The fluorescence of the cell is inspected soon after, typically the next day. At this point, two features of cellular fluorescence are noted: the intensity and the sub-cellular localization.

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The intensity should usually be at least as strong as that of unfused GFP in the cells. If it is not, the sequence or quality of the probe-DNA might be faulty, and should be carefully checked.

The sub-cellular localization is an indication of whether the probe is likely to perform well. If it localizes as expected for the gene in question, e.g. is excluded from the nucleus, it can immediately go on to a functional test. If the probe is not localized soon after the transfection procedure, it may be because of overexpression at this point in time, as the cell typically will have taken of very many copies of the plasmid, and localization will occur in time, e.g. within a few weeks, as plasmid copy number and expression level decreases. If localization does not occur after prolonged time, it may be because the fusion to GFP has destroyed a localization function, e.g. masked a protein sequence essential for interaction with its normal cellular anchor-protein. In this case the opposite fusion might work, e.g. if GeneX-GFP does not work, GFP-GeneX might, as two different parts of GeneX will be affected by the proximity to GFP. If this does not work, the proximity of GFP at either end might be a problem, and it could be attempted to increase the distance by incorporating a longer linker between GeneX and GFP in the DNA construct.

If there is no prior knowledge of localization, and no localization is observed, it may be because the probe should not be localized at this point, because such is the nature of the protein fused to GFP. It should then be subjected to a functional test.

In a functional test, the cells expressing the probe are treated with at least one compound known to perturb, usually by activating, the signalling pathway on which the probe is expected to report by redistributing itself within the cell. If the redistribution is as expected, e.g. if prior knowledge tell that it should translocate from location X to location Y, it has passed the first critical test. In this case it can go on to further characterization and quantification of the response.

If it does not perform as expected, it may be because the cell lacks at least one component of the signalling pathway, e.g. a cell surface receptor, or there is species incompatibility, e.g. if the probe is modelled on sequence information of a human geneproduct, and the cell is of hamster origin. In both instances one should identify other cell types for the testing process where these potential problems would not apply.

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If there is no prior knowledge about the pattern of redistribution, the analysis of the redistribution will have to be done in greater depth to identify what the essential and indicative features are, and when this is clear, it can go on to further characterization and quantification of the response. If no feature of redistribution can be identified, the problem might be as mentioned above, and the probe should be retested under more optimal cellular conditions.

If the probe does not perform under optimal cellular conditions it's back to the drawing board.

Developing an image-based assay technique

The process of developing an image-based redistribution assay begins with either the unplanned experimental observation that a redistribution phenomenon can be visualised, or the design of a probe specifically to follow a redistribution phenomenon already known to occur. In either event, the first and best exploratory technique is for a trained scientist or technician to observe the phenomenon. Even with the rapid advances in computing technology, the human eye-brain combination is still the most powerful pattern recognition system known, and requires no advance knowledge of the system in order to detect potentially interesting and useful patterns in raw data. This is especially if those data are presented in the form of images, which are the natural "data type" for human visual processing. Because human visual processing operates most effectively in a relatively narrow frequency range, i.e., we cannot see either very fast or very slow changes in our visual field, it may be necessary to record the data and play it back with either time dilation or time compression.

Some luminescence phenomena cannot be seen directly by the human eye. Examples include polarization and fluorescence lifetime. However, with suitable filters or detectors, these signals can be recorded as images or sequences of images and displayed to the human in the fashion just described. In this way, patterns can be detected and the same methods can be applied.

Once the redistribition has been determined to be a reproducible phenomenon, one or more data sets are generated for the purpose of developing a procedure for extracting the quantitative information from the data. In parallel, the biological and optical conditions are determined which will give the best quality raw data for the assay. This can become an iterative process; it may be necessary to develop a quantitative procedure in order to assess the effect on the assay of manipulating the assay conditions.

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The data sets are examined by a person or persons with knowledge of the biological phenomenon and skill in the application of image processing techniques. The goal of this exercise is to determine or at least propose a method which will reduce the image or sequence of images constituting the record of a "response" to a value corresponding to the degree of the response. Using either interactive image processing software or an image processing toolbox and a programming language, the method is encoded as a procedure or algorithm which takes the image or images as input and generates the degree of response (in any units) as its output. Some of the criteria for evaluating the validity of a particular procedure are:

- Does the degree of the response vary in a biologically significant fashion, i.e., does it show the known or putative dependence on the concentration of the stimulating agent or condition?
- Is the degree of response reproducible, i.e., does the same concentration or level of stimulating agent or condition give the same response with an acceptable variance?
- Is the dynamic range of the response sufficient for the purpose of the assay? If not,
 can a change in the procedure or one of its parameters improve the dynamic range?
- Does the procedure exhibit any clear "pathologies", i.e., does it give ridiculous values for the response if there are commonly occurring imperfections in the imaging process? Can these pathologies be eliminated, controlled, or accounted for?
- Can the procedure deal with the normal variation in the number and/or size of cells in an image?

In some cases the method may be obvious; in others, a number of possible procedures may suggest themselves. Even if one method appears clearly superior to others, optimisation of parameters may be required. The various procedures are applied to the data set and the criteria suggested above are determined, or the single procedure is applied repeatedly with adjustment of the parameter or parameters until the most satisfactory combination of signal, noise, range, etc. are arrived at. This is equivalent to the calibration of any type of single-channel sensor.

The number of ways of extracting a single value from an image are extremely large, and thus an intelligent approach must be taken to the initial step of reducing this number to a small, finite number of possible procedures. This is not to say that the procedure arrived at is

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necessarily the best procedure - but a global search for the best procedure is simply out of the question due to the sheer number of possibilities involved.

Image-based assays are no different than other assay techniques in that their usefulness is characterised by parameters such as the specificity for the desired component of the sample, the dynamic range, the variance, the sensitivity, the concentration range over which the assay will work, and other such parameters. While it is not necessary to characterise each and every one of these before using the assay, they represent the only way to compare one assay with another.

10 Example: Developing a Quantitative assay for GLUT4 Translocation

GLUT4 is a member of the class of glucose transporter molecules which are important in cellular glucose uptake. It is known to translocate to the plasma membrane under some conditions of stimulation of glucose uptake. The ability to visualize the glucose uptake response noninvasively, without actually measuring glucose uptake, would be a very useful assay for anyone looking for, for example, treatments for type II diabetes.

A CHO cell line which stably expressed the human insulin receptor was used as the basis for a new cell line which stably expressed a fusion between GLUT4 and GFP. This cell line was expected to show translocation of GLUT4 to the plasma membrane as visualized by the movement of the GFP. The translocation could definitely be seen in the form of the appearance of local increases in the fluorescence in regions of the plasma membrane which had a characteristic shape or pattern. This is shown in Figure 12.

These objects became known as "snircles", and the phenomenon of their appearance as "snircling". In order to quantitate their appearance, a method had to be found to isolate them as objects in the image field, and then enumerate them, measure their area, or determine some parameter about them which correlated in a dose-dependent fashion with the concentration of insulin to which the cells had been exposed. In order to separate the snircles, a binarization procedure was applied in which one copy of the image smoothed with a relatively severe gaussian kernel (sigma = 2.5) was subtracted from another copy to which only a relatively light gaussian smooth had been applied (sigma=0.5). The resultant image was rescaled to its min/max range, and an automatic threshold was applied to divide the image into two levels. The thresholded image contains a background of one value all found object with another value. The found objects were first filtered through a filter to remove objects far too

large and far too small to be snircles. The remaining objects, which represent snircles and other artifacts from the image with approximately the same size and intensity characteristics as snircles, are passed into a classification procedure which has been previously trained with many images of snircles to recognize snircles and exclude the other artifacts. The result of this procedure is a binary image which shows only the found snircles to the degree to which the classification procedure can accurately identify them. The total area of the snircles is then summed and this value is the quantitative measure of the degree of snircling for that image.

10 Definitions:

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In the present specification and claims, the term "an influence" covers any influence to which the cellular response comprises a redistribution. Thus, e.g., heating, cooling, high pressure, low pressure, humidifying, or drying are influences on the cellular response on which the resulting redistribution can be quantified, but as mentioned above, perhaps the most important influences are the influences of contacting or incubating the cell or cells with substances which are known or suspected to exert and influence on the cellular response involving a redistribution contribution. In another embodiment of the invention the influence could be substances from a compound drug library.

In the present context, the term "green fluorescent protein" is intended to indicate a protein which, when expressed by a cell, emits fluorescence upon exposure to light of the correct excitation wavelength (cf. [(Chalfie et al. 1994)]). In the following, GFP in which one or more amino acids have been substituted, inserted or deleted is most often termed "modified GFP". "GFP" as used herein includes wild-type GFP derived from the jelly fish Aequorea victoria and modifications of GFP, such as the blue fluorescent variant of GFP disclosed by Heim et al. (1994). Proc.Natl.Acad.Sci. 91:12501, and other modifications that change the spectral properties of the GFP fluorescence, or modifications that exhibit increased fluorescence when expressed in cells at a temperature above about 30°C described in PCT/DK96/00051, published as WO 97/11094 on 27 March 1997 and hereby incorporated by reference, and which comprises a fluorescent protein derived from Aequorea Green Fluorescent Protein (GFP) or any functional analogue thereof, wherein the amino acid in position 1 upstream from the chromophore has been mutated to provide an increase of fluorescence intensity when the

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fluorescent protein of the invention is expressed in cells. Preferred GFP variants are F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP. An especially preferred variant of GFP for use in all the aspects of this invention is EGFP (DNA encoding EGFP which is a F64L-S65T variant with codons optimized for expression in mammalian cells is available from Clontech, Palo Alto, plasmids containing the EGFP DNA sequence, cf. GenBank Acc. Nos. U55762, U55763).

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The term "intracellular signalling pathway" and "signal transduction pathway" are intended to indicate the coordinated intracellular processes whereby a living cell transduce an external or internal signal into cellular responses. Said signal transduction will involve an enzymatic reaction said enzymes include but are not limited to protein kinases, GTPases, ATPases, protein phosphatases, phospholipases. The cellular responses include but are not limited to gene transcription, secretion, proliferation, mechanical activity, metabolic activity, cell death.

The term "second messenger" is used to indicate a low molecular weight component invol-15 ved in the early events of intracellular signal transduction pathways.

The term "luminophore" is used to indicate a chemical substance which has the property of emitting light either inherently or upon stimulation with chemical or physical means. This includes but is not limited to fluorescence, bioluminescence, phosphorescence, chemiluminescence.

The term "mechanically intact living cell" is used to indicate a cell which is considered living according to standard criteria for that particular type of cell such as maintenance of normal membrane potential, energy metabolism, proliferative capability, and has not experienced any physically invasive treatment designed to introduce external substances into the cell such as microinjection.

The term "physiologically relevant", when applied to an experimentally determined redistribution of an intracellular component, as measured by a change in the luminescence properties or distribution, is used to indicate that said redistribution can be explained in terms of the underlying biological phenomenon which gives rise to the redistribution.

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Th terms "image processing" and "image analysis" are used to describe a large family of digital data analysis techniques or combination of such techniques which reduce ordered arrays of numbers (images) to quantitative information describing those ordered arrays of numbers. When said ordered arrays of numbers represent measured values from a physical process, the quantitative information derived is therefore a measure of the physical process.

The term "fluorescent probe" is used to indicate a fluorescent fusion polypeptide comprising a GFP or any functional part thereof which is N- or C-terminally fused to a biologically active polypeptide as defined herein, optionally via a peptide linker consisting of one or more amino acid residues, where the size of the linker peptide in itself is not critical as long as the desired functionality of the fluorescent probe is maintained. A fluorescent probe according to the invention is expressed in a cell and basically mimics the physiological behaviour of the biologically active polypeptide moiety of the fusion polypeptide.

The term "mammalian cell" is intended to indicate any living cell of mammalian origin. The cell may be an established cell line, many of which are available from The American Type Culture Collection (ATCC, Virginia, USA) or a primary cell with a limited life span derived from a mammalian tissue, including tissues derived from a transgenic animal, or a newly established immortal cell line derived froma mammalian tissue including transgenic tissues, or a hybrid cell or cell line derived by fusing different celltypes of mammalian origin e.g. hybridoma cell lines. The cells may optionally express one or more non-native gene products, e.g. receptors, enzymes, enzyme substrates, prior to or in addition to the fluorescent probe. Preferred cell lines include but are not limited to those of fibroblast origin, e.g. BHK, CHO, BALB, or of endothelial origin, e.g. HUVEC, BAE (bovine artery endothelial), CPAE (cow pulmonary artery endothelial) or of pancreatic origin, e.g. RIN, INS-1, MIN6, bTC3, aTC6, bTC6, HIT, or of hematopoietic origin, e.g. adipocyte origin, e.g. 3T3-L1, neuronal/neuroendocrine origin, e.g. AtT20, PC12, GH3, muscle origin, e.g. SKMC, A10, C2C12, renal origin, e.g. HEK 293, LLC-PK1.

The term "hybrid polypeptide" is intended to indicate a polypeptide which is a fusion of at least a portion of each of two proteins, in this case at least a portion of the green fluorescent protein, and at least a portion of a catalytic and/or regulatory domain of a protein kinase.

Furthermore a hybrid polypeptide is intended to indicate a fusion polypeptide comprising a

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GFP or at least a portion of the green fluorescent protein that contains a functional fluorophore, and at least a portion of a biologically active polypeptide as defined herein provided that said fusion is not the PKC α -GFP, PKC γ -GFP, and PKC ϵ -GFP disclosed by Schmidt et al.and Sakai et al., respectively. Thus, GFP may be N- or C-terminally tagged to a biologically active polypeptide, optionally via a linker portion or linker peptide consisting of a sequence of one or more amino acids. The hybrid polypeptide or fusion polypeptide may act as a fluorescent probe in intact living cells carrying a DNA sequence encoding the hybrid polypeptide under conditions permitting expression of said hybrid polypeptide.

The term "kinase" is intended to indicate an enzyme that is capable of phosphorylating a cellular component.

The term "protein kinase" is intended to indicate an enzyme that is capable of phosphorylating serine and/or threonine and/or tyrosine in peptides and/or proteins.

The term "phosphatase" is intended to indicate an enzyme that is capable of dephosphorylating phosphoserine and/or phosphothreonine and/or phosphotyrosine in peptides and/or proteins.

In the present context, the term "biologically active polypeptide" is intended to indicate a polypeptide affecting intracellular processes upon activation, such as an enzyme which is active in intracellular processes or a portion thereof comprising a desired amino acid sequence which has a biological function or exerts a biological effect in a cellular system. In the polypeptide one or several aminoacids may have been deleted, inserted or replaced to alter its biological function, e.g. by rendering a catalytic site inactive. Preferably, the biologically active polypeptide is selected from the group consisting of proteins taking part in an intracellular signalling pathway, such as enzymes involved in the intracellular phosphorylation and dephosphorylation processes including kinases, protein kinases and phosphorylases as defined herein, but also proteins making up the cytoskeleton play important roles in intracellular signal transduction and are therefore included in the meaning of "biologically active polypeptide" herein. More preferably, the biologically active polypeptide is a protein which according to its state as activated or non-activated changes localisation within the cell, preferably as an in-

termediary component in a signal transduction pathway. Included in this preferred group of biologically active polypeptides are cAMP dependent protein kinase A.

The term "a substance having biological activity" is intended to indicate any sample which has a biological function or exerts a biological effect in a cellular system. The sample may be a sample of a biological material such as a sample of a body fluid including blood, plasma, saliva, milk, urine, or a microbial or plant extract, an environmental sample containing pollutants including heavy metals or toxins, or it may be a sample containing a compound or mixture of compounds prepared by organic synthesis or genetic techniques.

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The phrase "any change in fluorescence" means any change in absorption properties, such as wavelength and intensity, or any change in spectral properties of the emitted light, such as a change of wavelength, fluorescence lifetime, intensity or polarisation, or any change in the intracellular localisation of the fluorophore. It may thus be localised to a specific cellular component (e.g. organelle, membrane, cytoskeleton, molecular structure) or it may be evenly distributed throughout the cell or parts of the cell.

The phrase "back-tracking of a signal transduction pathway" is intended to indicate.

The term "organism" as used herein indicates any unicellular or multicellular organism preferably originating from the animal kingdom including protozoans, but also organisms that are members of the plant kingdoms, such as algae, fungi, bryophytes, and vascular plants are included in this definition.

The term "nucleic acid" is intended to indicate any type of poly- or oligonucleic acid sequence, such as a DNA sequence, a cDNA sequence, or an RNA sequence.

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The term "biologically equivalent" as it relates to proteins is intended to mean that a first protein is equivalent to a second protein if the cellular functions of the two proteins may substitute for each other, e.g. if the two proteins are closely related isoforms encoded by different genes, if they are splicing variants, or allelic variants derived from the same gene, if they perform identical cellular functions in different cell types, or in different species. The term "biologically equivalent" as it relates to DNA is intended to mean that a first DNA sequ-

ence encoding a polypeptide is equivalent to a second DNA sequence encoding a polypeptide if the functional proteins encoded by the two genes are biologically equivalent.

The phrase "back-tracking of a signal transduction pathway" is intended to indicate a process for defining more precisely at what level a signal transduction pathway is affected, either by the influence of chemical compounds or a disease state in an organism. Consider a specific signal transduction pathway represented by the bioactive polypeptides A - B - C - D, with signal transduction from A towards D. When investigating all components of this signal transduction pathway compounds or disease states that influence the activity or redistribution of only D can be considered to act on C or downstream of C whereas compounds or disease states that influence the activity or redistribution of C and D, but not of A and B can be considered to act downstream of B.

The term "fixed cells" is used to mean cells treated with a cytological fixative such as glutaraldehyde or formaldehyde, treatments which serve to chemically cross-link and stabilize soluble and insoluble proteins within the structure of the cell. Once in this state, such proteins cannot be lost from the structure of the now-dead cell.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. CHO cells expressing the PKAc-F64L-S65T-GFP hybrid protein have been treated in HAM's F12 medium with 50 mM forskolin at 37°C. The images of the GFP fluorescence in these cells have been taken at different time intervals after treatment, which were: a) 40 seconds b) 60 seconds c) 70 seconds d) 80 seconds. The fluorescence changes from a punctate to a more even distribution within the (non-nuclear) cytoplasm.

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Figure 2. Time-lapse analysis of forskolin induced PKAc-F64L-S65T-GFP redistribution. CHO cells, expressing the PKAc-F64L-S65T-GFP fusion protein were analysed by time-lapse fluorescence microscopy. Fluorescence micrographs were acquired at regular intervals from 2 min before to 8 min after the addition of agonist. The cells were challenged with 1 mM forskolin immediately after the upper left image was acquired (t=0). Frames were collected at the following times: i) 0, ii) 1, iii) 2, iv) 3, v) 4 and vi) 5 minutes. Scale bar 10 mm.

Figure 3. Time-lapse analyses of PKAc-F64L-S65T-GFP redistribution in response to various agonists. The effects of 1 mM forskolin (A), 50 mM forskolin (B), 1mM dbcAMP (C) and 100 mM IBMX (D) (additions indicated by open arrows) on the localisation of the PKAc-F64L-S65T-GFP fusion protein were analysed by time-lapse fluorescence microscopy of CHO/PKAc-F64L-S65T-GFP cells. The effect of addition of 10 mM forskolin (open arrow), followed shortly by repeated washing with buffer (solid arrow), on the localisation of the PKAc-F64L-S65T-GFP fusion protein was analysed in the same cells (E). In a parallel experiment, the effect of adding 10 mM forskolin and 100 mM IBMX (open arrow) followed by repeated washing with buffer containing 100 mM IBMX (solid arrow) was analysed (F). Removing forskolin caused PKAc-F64L-S65T-GFP fusion protein to return to the cytoplasmic aggregates while this is prevented by the continued presence of IBMX (F). The effect of 100 nM glucagon (Fig 3G, open arrow) on the localisation of the PKAc-F64L-S65T-GFP fusion protein is also shown for BHK/GR, PKAc-F64L-S65T-GFP cells. The effect of 10 mM norepinephrine (H), solid arrow, on the localisation of the PKAc-F64L-S65T-GFP fusion protein was analysed similarly, in transiently transfected CHO, PKAc-F64L-S65T-GFP cells, pretreated with 10 mM forskolin, open arrow, to increase [cAMP], N.B. in Fig 3H the x-axis counts the image numbers, with 12 seconds between images. The raw data of each experiment consisted of 60 fluorescence micrographs acquired at regular intervals including several images acquired before the addition of buffer or agonist. The charts (A-G) each show a quantification of the response seen through all the 60 images, performed as described in analysis method 2. The change in total area of the highly fluorescent aggregates, relative to the initial area of fluorescent aggregates is plotted as the ordinate in all graphs in Figure 3, versus time for each experiment. Scale bar 10 mm.

Figure 4. Dose response curve (two experiments) for forskolin-induced redistribution of the PKAc-F64L-S65T-GFP fusion.

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Figure 5. Time from initiation of a response to half maximal ($t_{1/2max}$) and maximal (t_{max}) PKAc-F64L-S65T-GFP redistribution. The data was extracted from curves such as that shown in "Figure 2." All $t_{1/2max}$ and t_{max} values are given as mean±SD and are based on a total of 26-30 cells from 2-3 independent experiments for each forskolin concentration. Since the observed redistribution is sustained over time, the t_{max} values were taken as the earliest time point at which complete redistribution is reached. Note that the values do not relate to the degree of redistribution.

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Figure 6. Parallel dose response analyses of forskolin induced cAMP elevation and PKAc-F64L-S65T-GFP redistribution. The effects of buffer or 5 increasing concentrations of forskolin on the localisation of the PKAc-F64L-S65T-GFP fusion protein in CHO/PKAc-F64L-S65T-GFP cells, grown in a 96 well plate, were analysed as described above. Computing the ratio of the SD's of fluorescence micrographs taken of the same field of cells, prior to and 30 min after the addition of forskolin, gave a reproducible measure of PKAc-F64L-S65T-GFP redistribution. The graph shows the individual 48 measurements and a trace of their mean±s.e.m at each forskolin concentration. For comparison, the effects of buffer or 8 increasing concentrations of forskolin on [cAMP], was analysed by a scintillation proximity assay of cells grown under the same conditions. The graph shows a trace of the mean ± s.e.m of 4 experiments expressed in arbitrary units.

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Figure 7. BHK cells stably transfected with the human muscarinic (hM1) receptor and the PKCa-F64L-S65T-GFP fusion. Carbachol (100 mM added at 1.0 second) induced a transient redistribution of PKCa-F64L-S65T-GFP from the cytoplasm to the plasma membrane. Images were taken at the following times: a) 1 second before carbachol addition, b) 8.8 seconds after addition and c) 52.8 seconds after addition.

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Figure 8. BHK cells stably transfected with the hM1 receptor and PKCa-F64L-S65T-GFP fusion were treated with carbachol (1 mM, 10 mM, 100 mM). In single cells intracellular [Ca²+] was monitored simultaneously with the redistribution of PKCa-F64L-S65T-GFP. Dashed line indicates the addition times of carbachol. The top panel shows changes in the intracellular Ca²+ concentration of individual cells with time for each treatment. The middle panel shows changes in the average cytoplasmic GFP fluorescence for individual cells against time for each treatment. The bottom panel shows changes in the fluorescence of the periphery of single cells, within regions that specifically include the circumferential edge of a cell as seen in normal projection, the regions which offers best chance to monitor changes in the fluorescence intensity of the plasma membrane.

Figure 9. a) The hERK1-F64L-S65T-GFP fusion expressed in HEK293 cells treated with 100 mM of the MEK1 inhibitor PD98059 in HAM F-12 (without serum) for 30 minutes at 37 °C. The nuclei empty of fluorescence during this treatment.

- b) The same cells as in (a) following treatment with 10 % foetal calf serum for 15 minutes at 37 °C.
- c) Time profiles for the redistribution of GFP fluorescence in HEK293 cells following treatment with various concentrations of EGF in Hepes buffer (HAM F-12 replaced with Hepes buffer directly before the experiment). Redistribution of fluorescence is expressed as the change in the ratio value between areas in nucleus and cytoplasm of single cells. Each time profile is the mean for the changes seen in six single cells.
- d) Bar chart for the end-point measurements, 600 seconds after start of EGF treatments, of fluorescence change (nucleus:cytoplasm) following various concentrations of EGF.

Figure 10.

- a) The SMAD2-EGFP fusion expressed in HEK293 cells starved of serum overnight in HAM F-12. HAM F-12 was then replaced with Hepes buffer pH 7.2 immediately before the experiment. Scale bar is 10 mm.
- b) HEK 293 cells expressing the SMAD2-EGFP fusion were treated with various concentration of TGF-beta as indicated, and the redistribution of fluorescence monitored against time.

The time profile plots represent increases in fluorescence within the nucleus, normalised to starting values in each cell measured. Each trace is the time profile for a single cell nucleus.

c) A bar chart representing the end-point change in fluorescence within nuclei (after 850 seconds of treatment) for different concentrations of TGF-beta. Each bar is the value for a single nucleus in each treatment.

Figure 11. The VASP-F64L-S65T-GFP fusion in CHO cells stably transfected with the human insulin receptor. The cells were starved for two hours in HAM F-12 without serum, then treated with 10% foetal calf serum. The image shows the resulting redistribution of fluorescence after 15 minutes of treatment. GFP fluorescence becomes localised in structures identified as focal adhesions along the length of actin stress fibres.

Figure 12. Time lapse recording GLUT4-GFP redistribution in CHO-HIR cells. Time indicates minutes after the addition of 100 nM insulin.

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EXAMPLE 1

5 Construction, testing and implementation of an assay for cAMP based on PKA activation in real time within living cells.

Useful for monitoring the activity of signalling pathways which lead to altered concentrations of cAMP, e.g. activation of G-protein coupled receptors which couple to G-proteins of the G_s or G_i class.

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The catalytic subunit of the murine cAMP dependent protein kinase (PKAc)was fused C-terminally to a F64L-S65T derivative of GFP. The resulting fusion (PKAc-F64L-S65T-GFP) was used for monitoring *in vivo* the translocation and thereby the activation of PKA.

Construction of the PKAc-F64L-S65T-GFP fusion:

15 Convenient restriction endonuclease sites were introduced into the cDNAs encoding murine PKAc (Gen Bank Accession number: M12303) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) by polymerase chain reaction (PCR). The PCR reactions were performed according to standard protocols with the following primers:

5'PKAc: TTggACACAAgCTTTggACACCCTCAggATATgggCAACgCCgCCgCCGCCAAg (SEQ ID NO:3),

3'PKAc: gTCATCTTCTCgAgTCTTTCAggCgCgCCCAAACTCAgTAAACTCCTTgCCACAC (SEQ ID NO:4),

5'GFP: TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAAGATTTTC (SEQ ID NO:1),

25 3'GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgCCATgT (SEQ ID NO:2).

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The PKAc amplification product was then digested with HindIII+AscI and the F64L-S65T-GFP product with AscI+XhoI. The two digested PCR products were subsequently ligated with a HindIII+XhoI digested plasmid (pZeoSV® mammalian expression vector, Invitrogen, San Diego, CA, USA). The resulting fusion construct (SEQ ID NO:68 & 69) was under control of the SV40 promoter.

Transfection and cell culture conditions.

Chinese hamster ovary cells (CHO), were transfected with the plasmid containing the PKAc-F64L-S65T-GFP fusion using the calcium phosphate precipitate method in HEPES-buffered saline (Sambrook *et al.*, 1989). Stable transfectants were selected using 1000 mg Zeocin/ml (Invitrogen) in the growth medium (DMEM with 1000 mg glucose/l, 10 % fetal bovine serum (FBS), 100 mg penicillin-streptomycin mixture ml⁻¹, 2 mM L-glutamine purchased from Life Technologies Inc., Gaithersburg, MD, USA). Untransfected CHO cells were used as the control. To assess the effect of glucagon on fusion protein translocation, the PKAc-F64L-S65T-GFP fusion was stably expressed in baby hamster kidney cells overexpressing the human glucagon receptor (BHK/GR cells) Untransfected BHK/GR cells were used as the control. Expression of GR was maintained with 500 mg G418/ml (*Neo* marker) andPKAc-F64L-S65T-GFP was maintained with 500 mg Zeocin/ml (*Sh ble* marker). CHO cells were also simultaneously co-transfected with vectors containing the PKAc-F64L-S65T-GFP fusion and the human a2a adrenoceptor (hARa2a).

For fluorescence microscopy, cells were allowed to adhere to Lab-Tek chambered coverglasses (Nalge Nunc Int., Naperville, IL, USA) for at least 24 hours and cultured to about 80% confluence. Prior to experiments, the cells were cultured over night without selection pressure in HAM F-12 medium with glutamax (Life Technologies), 100 mg penicillinstreptomycin mixture ml⁻¹ and 0.3 % FBS. This medium has low autofluorescence enabling fluorescence microscopy of cells straight from the incubator.

Monitoring activity of PKA activity in real time:

Image aquisition of live cells were gathered using a Zeiss Axiovert 135M fluorescence microscope fitted with a Fluar 40X, NA: 1.3 oil immersion objective and coupled to a Photometrics CH250 charged coupled device (CCD) camera. The cells were illuminated with a 100 W HBO arc lamp. In the light path was a 470±20 nm excitation filter, a 510 nm dichroic mirror

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and a 515±15 nm emission filter for minimal image background. The cells were kept and monitored to be at 37°C with a custom built stage heater.

Images were processed and analyzed in the following manner:.

Method 1: Stepwise procedure for quantitation of translocation of PKA:

- 1. The image was corrected for dark current by performing a pixel-by-pixel subtraction of a dark image (an image taken under the same conditions as the actual image, except the camera shutter is not allowed to open).
 - 2. The image was corrected for non-uniformity of the illumination by performing a pixel-bypixel ratio with a flat field correction image (an image taken under the same conditions as the actual image of a uniformly fluorescent specimen).
 - 3. The image histogram, i.e., the frequency of occurrence of each intensity value in the image, was calculated.
 - 4. A smoothed, second derivative of the histogram was calculated and the second zero is determined. This zero corresponds to the inflection point of the histogram on the high side of the main peak representing the bulk of the image pixel values.
 - 5. The value determined in step 4 was subtracted from the image. All negative values were discarded.
 - 6. The variance (square of the standard deviation) of the remaining pixel values was determined. This value represents the "response" for that image.
- 20 7. Scintillation proximity assay (SPA) for independent quantitation of cAMP:

Method 2: Alternative method for quantitation of PKA redistribution:

- 1. The fluorescent aggregates are segmented from each image using an automatically found threshold based on the maximisation of the information measure between the object and background. The *a priori* entropy of the image histogram is used as the information measure.
 - 2. The area of each image occupied by the aggregates is calculated by counting pixels in the segmented areas.
- 3. The value obtained in step 2 for each image in a series, or treatment pair, is normalised to the value found for the first (unstimulated) image collected. A value of zero (0) indicates no redistribution of fluorescence from the starting condition. A value of one (1) by this method equals full redistribution.
- 15 Cells were cultured in HAM F-12 medium as described above, but in 96-well plates. The medium was exchanged with Ca²⁺-HEPES buffer including 100 mM IBMX and the cells were stimulated with different concentrations of forskolin for 10 min. Reactions were stopped with addition of NaOH to 0.14 M and the amount of cAMP produced was measured with the cAMP-SPA kit, RPA538 (Amersham) as described by the manufacturer.

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Manipulating intracellular levels of cAMP to test the PKAc-F64L-S65T-GFP fusion.

The following compounds were used to vary cAMP levels: Forskolin, an activator of adenylate cyclase; dbcAMP, a membrane permeable cAMP analog which is not degraded by phosphodiesterase; IBMX, an inhibitor of phosphodiesterase.

- CHO cells stably expressing the PKAc-F64L-S65T-GFP, showed a dramatic translocation of the fusion protein from a punctate distribution to an even distribution throughout the cytoplasm following stimulation with 1 mM forskolin (n=3), 10 mM forskolin (n=4) and 50 mM forskolin (n=4) (Fig 1), or dbcAMP at 1mM (n=6).
 - Fig. 2 shows the progression of response in time following treatment with 1 mM forskolin.

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Fig. 3 gives a comparison of the average temporal profiles of fusion protein redistribution and a measure of the extent of each response to the three forskolin concentrations (Fig. 3A, E, B), and to 1 mM dbcAMP (fig 3C) which caused a similar but slower response, and to addition of 100 mM IBMX (n=4, Fig. 3D) which also caused a slow response, even in the absence of adenylate cyclase stimulation. Addition of buffer (n=2) had no effect (data not shown).

As a control for the behavior of the fusion protein, F64L-S65T-GFP alone was expressed in CHO cells and these were also given 50 mM forskolin (n=5); the uniform diffuse distribution characteristic of GFP in these cells was unaffected by such treatment (data not shown).

The forskolin induced translocation of PKAc-F64L-S65T-GFP showed a dose-response relationship (Fig 4 and 6), see quantitative procedures above.

Reversibility of PKAc-F64L-S65T-GFP translocation.

The release of the PKAc probe from its cytoplasmic anchoring hotspots was reversible. Washing the cells repeatedly (5-8 times) with buffer after 10µM forskolin treatment completely restored the punctate pattern within 2-5 min (n=2, Fig. 3E). In fact the fusion protein returned to a pattern of fluorescent cytoplasmic aggregates virtually indistinguishable from that observed before forskolin stimulation.

To test whether the return of fusion protein to the cytoplasmic aggregates reflected a decreased [cAMP], cells were treated with a combination of 10 mM forskolin and 100 mM IBMX (n=2) then washed repeatedly (5-8 times) with buffer containing 100 mM IBMX (Fig. 3F). In these experiments, the fusion protein did not return to its prestimulatory localization after removal of forskolin.

25 Testing the PKA-F64L-S65T-GFP probe with physiologically relevant agents.

To test the probe's response to receptor activation of adenylate cyclase, BHK cells stably transfected with the glucagon receptor and the PKA-F64L-S65T-GFP probe were exposed to glucagon stimulation. The glucagon receptor is coupled to a G_s protein which activates adenylate cyclase, thereby increasing the cAMP level. In these cells, addition of 100 nM glucagon (n=2) caused the release of the PKA-F64L-S65T-GFP probe from the cytoplasmic aggregates and a resulting translocation of the fusion protein to a more even cytoplasmic

distribution within 2-3 min (Fig. 3G). Similar but less pronounced effects were seen at lower glucagon concentrations (n=2, data not shown). Addition of buffer (n=2) had no effect over time (data not shown).

Transiently transfected CHO cells expressing hARa2a and the PKA-F64L-S65T-GFP probe were treated with 10 mM forskolin for 7.5 minutes, then, in the continued presence of forskolin, exposed to 10 mM norepinephrine to stimulate the exogenous adrenoreceptors, which couple to a G₁ protein, which inhibit adenylate cyclase. This treatment led to reappearance of fluorescence in the cytoplasmic aggregates indicative of a decrease in [cAMP]₁ (Fig. 3H).

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Fusion protein translocation correlated with [cAMP]_i

As described above, the time it took for a response to come to completion was dependent on the forskolin dose (Fig. 5) In addition the degree of responses was also dose dependent. To test the PKA-F64L-S65T-GFP fusion protein translocation in a semi high through-put system, CHO cells stably transfected with the PKA-F64L-S65T-GFP fusion was stimulated with buffer and 5 increasing doses of forskolin (n=8). Using the image analysis algorithm described above (Method 1), a dose response relationship was observed in the range from 0.01-50 mM forskolin (Fig. 6). A half maximal stimulation was observed at about 2 mM forskolin. In parallel, cells were stimulated with buffer and 8 increasing concentrations of forskolin (n=4) in the range 0.01-50 mM. The amount of cAMP produced was measured in an SPA assay. A steep increase was observed between 1 and 5 mM forskolin coincident with the steepest part of the curve for fusion protein translocation (also Fig. 6)

25 EXAMPLE 2

Quantitation of redistribution in real-time within living cells.

Probe for detection of PKC activity in real time within living cells:

Construction of PKC-GFP fusion:

The probe was constructed by ligating two restriction enzyme treated polymerase chain reaction (PCR) amplification products of the cDNA for murine PKCα (GenBank Accession number: M25811) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) respectively. Taq® polymerase and the following oligonucleotide primers were used for PCR;

5 5'mPKCa: TTggACACAAgCTTTggACACCCTCAggATATggCTgACgTTTACCCggCCAACg (SEQ ID NO:5),

3'mPKCa: gTCATCTTCTCgAgTCTTTCAggCgCgCCCTACTgCACTTTgCAAgATTgggTgC (SEQ ID NO:6),

5'F64L-S65T-GFP: TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAACTT10 TTC (SEQ ID NO:1),

3'F64L-S65T-GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgC-CATgT (SEQ ID NO:2).

The hybrid DNA strand was inserted into the pZeoSV® mammalian expression vector as a HindIII-Xhol casette as described in example 1.

15 Cell Culture:

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BHK cells expressing the human M1 receptor under the control of the inducible metallothionine promoter and maintained with the dihydrofolate reductase marker were transfected with the PKC α -F64L-S65T-GFP probe using the calcium phosphate precipitate method in HEPES buffered saline (HBS [pH 7.10]). Stable transfectants were selected using 1000 µg Zeocin®/ml in the growth medium (DMEM with 1000 mg glucose/l, 10 % foetal bovine serum (FBS), 100 mg penicillin-streptomycin mixture ml-1, 2 mM l-glutamine). The hM1 receptor and PKC α -F64L-S65T-GFP fusion protein were maintained with 500 nM methotrexate and 500 µg Zeocin®/ml respectively. 24 hours prior to any experiment, the cells were transferred to HAM F-12 medium with glutamax, 100 µg penicillin-streptomycin mixture ml-1 and 0.3 % FBS. This medium relieves selection pressure, gives a low induction of signal transduction pathways and has a low autofluorescence at the relevant wavelength enabling fluorescence microscopy of cells straight from the incubator.

Monitoring the PKC activity in real time:

Digital images of live cells were gathered using a Zeiss Axiovert 135M fluorescence microscope fitted with a 40X, NA: 1.3 oil immersion objective and coupled to a Photometrics

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CH250 charged coupled device (CCD) camera. The cells were illuminated with a 100 W arc lamp. In the light path was a 470±20 nm excitation filter, a 510 nm dichroic mirror and a 515±15 nm emission filter for minimal image background. The cells were kept and monitored to be at 37°C with a custom built stage heater.

5 Images were analyzed using the IPLab software package for Macintosh.

Upon stimulation of the M1-BHK cells, stably expressing the PKCα-F64L-S65T-GFP fusion, with carbachol we observed a dose-dependent transient translocation from the cytoplasm to the plasma membrane (Fig. 7a,b,c). Simultaneous measurement of the cytosolic free calcium concentration shows that the carbachol-induced calcium mobilisation precedes the translocation (Fig. 8).

Stepwise procedure for quantitation of translocation of PKC:

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- 1. The image was corrected for dark current by performing a pixel-by-pixel subtraction of a dark image (an image taken under the same conditions as the actual image, except the camera shutter is not allowed to open).
- 2. The image was corrected for non-uniformity of the illumination by performing a pixel-by-15 pixel ratio with a flat field correction image (an image taken under the same conditions as the actual image of a uniformly fluorescent specimen).
 - 3. A copy of the image was made in which the edges are identified. The edges in the image are found by a standard edge-detection procedure – convolving the image with a kernel which removes any large-scale unchanging components (i.e., background) and accentuates any small-scale changes (i.e., sharp edges). This image was then converted to a binary image by threshholding. Objects in the binary image which are too small to represent the edges of cells were discarded. A dilation of the binary image was performed to close any gaps in the image edges. Any edge objects in the image which were in contact with the borders of the image are discarded. This binary image represents the edge mask.
 - Another copy of image was made via the procedure in step 3. This copy was further processed to detect objects which enclose "holes" and setting all pixels inside the holes to the binary value of the edge, i.e., one. This image represents the whole cell mask.
 - The original image was masked with the edge mask from step 3 and the sum total of all pixel values is determined.

- 6. The original image was masked with the whole cell mask from step 4 and the sum total of all pixel values was determined.
- 7. The value from step 5 was divided by the value from step 6 to give the final result, the fraction of fluorescence intensity in the cells which was localized in the edges.

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EXAMPLE 3

Probes for detection of mitogen activated protein kinase Erk1 redistribution.

Useful for monitoring signalling pathways involving MAPK, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Erk1, a serine/threonine protein kinase, is a component of a signalling pathway which is activated by e.g. many growth factors.

Probes for detection of ERK-1 activity in real time within living cells:

- The extracellular signal regulated kinase (ERK-1, a mitogen activated protein kinase, MAPK) is fused N- or C-terminally to a derivative of GFP. The resulting fusions expressed in different mammalian cells are used for monitoring *in vivo* the nuclear translocation, and thereby the activation, of ERK1 in response to stimuli that activate the MAPK pathway.
 - a) Construction of murine ERK1 F64L-S65T-GFP fusion:
- Convenient restriction endonuclease sites are introduced into the cDNAs encoding murine ERK1 (GenBank Accession number: Z14249) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) by polymerase chain reaction (PCR). The PCR reactions are performed according to standard protocols with the following primers:

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5'F64L-S65T-GFP: TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAAGAACTT-TTC (SEQ ID NO:1)

5 3'F64L-S65T-GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgC-CATgT (SEQ ID NO:2)

To generate the mERK1-F64L-S65T-GFP (SEQ ID NO:56 & 57) fusion the ERK1 amplification product is digested with HindIII+AscI and the F64L-S65T-GFP product with AscI+Xhol. To generate the F64L-S65T-GFP-mERK1 fusion the ERK1 amplification product is then digested with HindIII+Bsu36I and the F64L-S65T-GFP product with Bsu36I+Xhol.The two pairs of digested PCR products are subsequently ligated with a HindIII+Xhol digested plasmid (pZeoSV® mammalian expression vector, Invitrogen, San Diego, CA, USA). The resulting fusion constructs are under control of the SV40 promoter.

b) The human Erk1 gene (GenBank Accession number: X60188) was amplified using PCR according to standard protocols with primers Erk1-top (SEQ ID NO:9) and Erk1-bottom/+stop (SEQ ID NO:10). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Erk1 fusion
 (SEQ ID NO:38 &39) under the control of a CMV promoter.

The plasmid containing the EGFP-Erk1 fusion was transfected into HEK293 cells employing the FUGENE transfection reagent (Boehringer Mannheim). Prior to experiments the cells were grown to 80%-90% confluency 8 well chambers in DMEM with 10% FCS. The cells were washed in plain HAM F-12 medium (without FCS), and then incubated for 30-60 minutes in plain HAM F-12 (without FCS) with 100 micromolar PD98059, an inhibitor of MEK1, a kinase which activates Erk1; this step effectively empties the nucleus of EGFP-Erk1. Just before starting the experiment, the HAM F-12 was replaced with Hepes buffer following a wash with Hepes buffer. This removes the PD98059 inhibitor; if blocking of MEK1 is still wanted (e.g. in control experiments), the inhibitor is included in the Hepes buffer.

The experimental setup of the microscope was as described in example 1.

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60 images were collected with 10 seconds between each, and with the test compound added after image number 10.

Addition of EGF (1-100 nM) caused within minutes a redistribution of EGFP-Erk1 from the cytoplasm into the nucleus (Fig. 9a,b).

The response was quantitated as described below and a dose-dependent relationship between EGF concentration and nuclear translocation of EGFP-Erk1 was found (Fig. 9c,d). Reditribution of GFP fluorescence is expressed in this example as the change in the ratio value between areas in nuclear versus cytoplasmic compartments of the cell. Each time profile is the average of nuclear to cytoplasmic ratios from six cells in each treatment.

EXAMPLE 4:

Probes for detection of Erk2 redistribution.

Useful for monitoring signalling pathways involving MAPK, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Erk2, a serine/threonine protein kinase, is closely related to Erk1 but not identical; it is a component of a signalling pathway which is activated by e.g. many growth factors.

- a) The rat Erk2 gene (GenBank Accession number: M64300) was amplified using PCR according to standard protocols with primers Erk2-top (SEQ ID NO:11) and Erk2-bottom/+stop (SEQ ID NO:13) The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-Erk2 fusion (SEQ ID NO:40 &41) under the control of a CMV promoter.
- b) The rat Erk2 gene (GenBank Accession number: M64300) was amplified using PCR according to standard protocols with primers (SEQ ID NO:11) Erk2-top and Erk2-bottom/-stop (SEQ ID NO:12). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces an Erk2-EGFP fusion (SEQ ID NO:58 &59) under the control of a CMV promoter.

The resulting plasmids were transfected into CHO cells and BHK cells. The cells were grown under standard conditions. Prior to experiments, the cells were starved in medium without serum for 48-72 hours. This led to a predominantly cytoplasmic localization of both probes, especially in BHK cells. 10% fetal calf serum was added to the cells and the fluorescence of the cells was recorded as explained in example 3. Addition of serum caused the probes to redistribute into the nucleus within minutes of addition of serum.

EXAMPLE 5:

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10 Probes for detection of Smad2 redistribution.

Useful for monitoring signalling pathways activated by some members of the transforming growth factor-beta family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Smad 2, a signal transducer, is a component of a signalling pathway which is induced by some members of the TGFbeta family of cytokines.

- a) The human Smad2 gene (GenBank Accession number: AF027964) was amplified using PCR according to standard protocols with primers Smad2-top (SEQ ID NO:24) and Smad2-bottom/+stop (SEQ ID NO:26). The PCR product was digested with restriction enzymes E-coR1 and Acc65I, and ligated into pEGFP-C1 (Clontech; Palo Alto; GenBank Accession number U55763) digested with EcoR1 and Acc65I. This produces an EGFP-Smad2 fusion (SEQ ID NO:50&51) under the control of a CMV promoter.
- b) The human Smad2 gene (GenBank Accession number: AF027964) was amplified using PCR according to standard protocols with primers Smad2-top (SEQ ID NO:24) and Smad2-bottom/-stop (SEQ ID NO:25). The PCR product was digested with restriction enzymes E-coR1 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and Acc65I. This produces a Smad2-EGFP fusion (SEQ ID NO:74 &75) under the control of a CMV promoter.
- The plasmid containing the EGFP-Smad2 fusion was transfected into HEK293 cells, where it showed a cytoplasmic distribution. Prior to experiments the cells were grown in 8 well Nunc

chambers in DMEM with 10% FCS to 80% confluency and starved overnight in HAM F-12 medium without FCS.

For experiments, the HAM F-12 medium was replaced with Hepes buffer pH 7.2.

The experimental setup of the microscope was as described in example 1.

90 images were collected with 10 seconds between each, and with the test compound added after image number 5.

After serum starvation of cells, each nucleus contains less GFP fluorescence than the surrounding cytoplasm (Fig. 10a). Addition of TGFbeta caused within minutes a redistribution of EGFP-Smad2 from the cytoplasma into the nucleus (Fig. 10b).

The redistribution of fluorescence within the treated cells was quantified simply as the fractional increase in nuclear fluorescence normalised to the starting value of GFP fluorescence in the nucleus of each unstimulated cell.

15 EXAMPLE 6:

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Probe for detection of VASP redistribution.

Useful for monitoring signalling pathways involving rearrangement of cytoskeletal elements, e.g. to identify compounds which modulate the activity of the pathway in living cells.

VASP, a phosphoprotein, is a component of cytoskeletal structures, which redistributes in response to signals which affect focal adhesions.

a) The human VASP gene (GenBank Accession number: Z46389) was amplified using PCR according to standard protocols with primers VASP-top (SEQ ID NO:94) and VASP-bottom/+stop (SEQ ID NO:95). The PCR product was digested with restriction enzymes Hind3 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Hind3and BamH1. This produces an EGFP-VASP fusion (SEQ ID NO:124 &125) under the control of a CMV promoter.

The resulting plasmid was transfected into CHO cells expressing the human insulin receptor using the calcium-phosphate transfection method. Prior to experiments, cells were grown in 8 well Nunc chambers and starved overnight in medium without FCS.

Experiments are performed in a microscope setup as described in example 1.

10% FCS was added to the cells and images were collected. The EGFP-VASP fusion was redistributed from a somewhat even distribution near the periphery into more localized structures, identified as focal adhesion points (Fig. 11).

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A large number of further GFP fusions have been made or are in the process of being made, as apparent from the following Examples 7-22 which also suggest suitable host cells and substances for activation of the cellular signalling pathways to be monitored and analyzed.

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EXAMPLE 7:

Probe for detection of actin redistribution.

Useful for monitoring signalling pathways involving rearrangement or formation of actin filaments, e.g. to identify compounds which modulate the activity of pathways leading to cytoskeletal rearrangements in living cells.

Actin is a component of cytoskeletal structures, which redistributes in response to very many cellular signals.

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The actin binding domain of the human alpha-actinin gene (GenBank Accession number: X15804) was amplified using PCR according to standard protocols with primers ABD-top (SEQ ID NO:90) and ABD-bottom/-stop (SEQ ID NO:91). The PCR product was digested with restriction enzymes Hind3 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Hind3 and BamH1. This produced an actin-binding-domain-EGFP fusion (SEQ ID NO:128 &129) under the control of a CMV promoter.

The resulting plasmid was transfected into CHO cells expressing the human insulin receptor. Cells were stimulated with insulin which caused the actin binding domain-EGFP probe to become redistributed into morphologically distinct membrane-associated structures.

Example 8:

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Probes for detection of p38 redistribution.

Useful for monitoring signalling pathways responding to various cellular stress situations, e.g. to identify compounds which modulate the activity of the pathway in living cells, or as a counterscreen.

p38, a serine/thronine protein kinase, is a component of a stress-induced signalling pathway which is activated by many types of cellular stress, e.g. TNFalpha, anisomycin, UV and mitomycin C.

- a) The human p38 gene (GenBank Accession number: L35253) was amplified using PCR according to standard protocols with primers p38-top (SEQ ID NO:14) and p38-bottom/+stop (SEQ ID NO: 16). The PCR product was digested with restriction enzymes
 Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produced an EGFP-p38 fusion (SEQ ID NO:46 &47) under the control of a CMV promoter.
 - b) The human p38 gene (GenBank Accession number: L35253) was amplified using PCR according to standard protocols with primers p38-top (SEQ ID NO:13) and p38-bottom/-stop (SEQ ID NO:15). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a p38-EGFP fusion (SEQ ID NO:64 &65) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. HEK293, in which the EGFP-p38 probe and/or the p38-EGFP probe should change its cellular distribution from predominantly cytoplasmic to nuclear within minutes in response to activation of the signal-ling pathway with e.g. anisomycin.

Example 9:

30 Probes for detection of Jnk1 redistribution.

Useful for monitoring signalling pathways responding to various cellular stress situations, e.g. to identify compounds which modulate the activity of the pathway in living cells, or as a counterscreen.

Jnk1, a serine/threonine protein kinase, is a component of a stress-induced signalling pathway different from the p38 described above, though it also is activated by many types of cellular stress, e.g. TNFalpha, anisomycin and UV.

- a) The human Jnk1 gene (GenBank Accession number: L26318) was amplified using PCR according to standard protocols with primers Jnk-top (SEQ ID NO:17) and Jnk-bottom/+stop (SEQ ID NO:19). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produced an EGFP-Jnk1 fusion (SEQ ID NO:44 &45) under the control of a CMV promoter.
- b) The human Jnk1 gene (GenBank Accession number: L26318) was amplified using PCR according to standard protocols with primers Jnk-top (SEQ ID NO:17) and Jnk-bottom/-stop (SEQ ID NO:18). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a Jnk1-EGFP fusion (SEQ ID NO:62 &63) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. HEK293, in which the EGFP-Jnk1 probe and/or the Jnk1-EGFP probe should change its cellular distribution from predominantly cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. anisomycin.

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Example 10:

Probes for detection of PKG redistribution.

Useful for monitoring signalling pathways involving changes in cyclic GMP levels, e.g. to identify compounds which modulate the activity of the pathway in living cells.

30 PGK, a cGMP-dependent serine/threonine protein kinase, mediates the guanylyl-cyclase/cGMP signal.

- a) The human PKG gene (GenBank Accession number: Y07512) is amplified using PCR according to standard protocols with primers PKG-top (SEQ ID NO:81) and PKG-bottom/+stop (SEQ ID NO:83). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-PKG fusion (SEQ ID NO:134 &135) under the control of a CMV promoter.
- b) The human PKG gene (GenBank Accession number: Y07512) is amplified using PCR according to standard protocols with primers PKG-top (SEQ ID NO:81) and PKG-bottom/-stop (SEQ ID NO: 82). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces a PKG-EGFP fusion (SEQ ID NO:136 &137) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. A10, in which the EGFP-PKG probe and/or the PKG-EGFP probe should change its cellular distribution from cyto-plasmic to one associated with cytoskeletal elements within minutes in response to treatment with agents which raise nitric oxide (NO) levels.

Example 11:

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20 Probes for detection of IkappaB kinase redistribution.

Useful for monitoring signalling pathways leading to NFkappaB activation, e.g. to identify compounds which modulate the activity of the pathway in living cells.

IkappaB kinase, a serine/threonine kinase, is a component of a signalling pathway which is activated by a variety of inducers including cytokines, lymphokines, growth factors and stress.

a) The alpha subunit of the human IkappaB kinase gene (GenBank Accession number: AF009225) is amplified using PCR according to standard protocols with primers IKK-top (SEQ ID NO:96) and IKK-bottom/+stop (SEQ ID NO:98). The PCR product is digested with restriction enzymes EcoR1 and Acc65I, and ligated into pEGFP-C1 (Clontech, Palo Alto;

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GenBank Accession number U55763) digested with EcoR1and Acc65I. This produces an EGFP-IkappaB-kinase fusion (SEQ ID NO:120 &121) under the control of a CMV promoter.

b) The alpha subunit of the human IkappaB kinase gene (GenBank Accession number: AF009225) is amplified using PCR according to standard protocols with primers IKK-top (SEQ ID NO:96) and IKK-bottom/-stop (SEQ ID NO:97). The PCR product is digested with restriction enzymes EcoR1 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and Acc65I. This produces an IkappaB-kinase-EGFP fusion (SEQ ID NO:122 &123) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-lkappaB-kinase probe and/or the lkappaB-kinase-EGFP probe should achieve a more cytoplasmic distribution within seconds following stimulation with e.g. TNFalpha.

Example 12:

Probes for detection of CDK2 redistribution.

Useful for monitoring signalling pathways of the cell cycle, e.g. to identify compounds which modulate the activity of the pathway in living cells.

CDK2, a cyclin-dependent serine/threonine kinase, is a component of the signalling system which regulates the cell cycle.

- a) The human CDK2 gene (GenBank Accession number: X61622) is amplified using PCR according to standard protocols with primers CDK2-top (SEQ ID NO:102) and CDK2-bottom/+stop (SEQ ID NO: 104). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-CDK2 fusion (SEQ ID NO:114 &115) under the control of a CMV promoter.
 - b) The human CDK2 gene (GenBank Accession number: X61622) is amplified using PCR according to standard protocols with primers CDK2-top (SEQ ID NO:102) and CDK2-bottom/-stop (SEQ ID NO:103). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces a CDK2-EGFP fusion (SEQ ID NO:112 &113) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. HEK293 in which the EGFP-CDK2 probe and/or the CDK2-EGFP probe should change its cellular distribution from cytoplasmic in contact-inhibited cells, to nuclear location in response to activation with a number of growth factors, e.g. IGF.

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Example 13:

Probes for detection of Grk5 redistribution.

Useful for monitoring signalling pathways involving desensitization of G-protein coupled receptors, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Grk5, a G-protein coupled receptor kinase, is a component of signalling pathways involving membrane bound G-protein coupled receptors.

- a) The human Grk5 gene (GenBank Accession number: L15388) is amplified using PCR according to standard protocols with primers Grk5-top (SEQ ID NO:27) and Grk5-bottom/+stop (SEQ ID NO:29). The PCR product is digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Grk5 fusion (SEQ ID NO:42 &43) under the control of a CMV promoter.
- b) The human Grk5 gene (GenBank Accession number: L15388) is amplified using PCR according to standard protocols with primers Grk5-top (SEQ ID NO:27) and Grk5-bottom/-stop (SEQ ID NO:28). The PCR product is digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produces a Grk5-EGFP fusion (SEQ ID NO:60 &61) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. HEK293 expressing a rat dopamine D1A receptor, in which the EGFP-Grk5 probe and/or the Grk5-EGFP probe should change its cellular distribution from predominantly cytoplasmic to peripheral in response to activation of the signalling pathway with e.g. dopamine.
- 30 Example 14:

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Probes for detection of Zap70 redistribution.

Useful for monitoring signalling pathways involving the T cell receptor, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Zap70, a tyrosine kinase, is a component of a signalling pathway which is active in e.g. T-cell differentiation.

- a) The human Zap70 gene (GenBank Accession number: L05148) is amplified using PCR according to standard protocols with primers Zap70-top (SEQ ID NO:105) and Zap70-bottom/+stop (SEQ ID NO:107). The PCR product is digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-C1 (GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Zap70 fusion (SEQ ID NO:108 &109) under the control of a CMV promoter.
- b) The human Zap70 gene (GenBank Accession number: L05148) is amplified using PCR according to standard protocols with primers Zap70-top (SEQ ID NO:105) and Zap70-top (SEQ ID NO:105). The PCR product is digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produces a Zap70-EGFP fusion (SEQ ID NO:110 &111) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the

 EGFP-Zap70 probe and/or the Zap70-EGFP probe should change its cellular distribution
 from cytoplasmic to membrane-associated within seconds in response to activation of the T
 cell receptor signalling pathway with e.g. antibodies to CD3epsilon.

Example 15:

25 Probes for detection of p85 redistribution.

Useful for monitoring signalling pathways involving PI-3 kinase, e.g. to identify compounds which modulate the activity of the pathway in living cells.

p85alpha is the regulatory subunit of Pl3-kinase which is a component of many pathways involving membrane-bound tyrosine kinase receptors and G-protein-coupled receptors.

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- a) The human p85alpha gene (GenBank Accession number: M61906) was amplified using PCR according to standard protocols with primers p85-top-C (SEQ ID NO:22) and p85-bottom/+stop (SEQ ID NO:23). The PCR product was digested with restriction enzymes Bgl2 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Bgl2 and BamH1. This produced an EGFP-p85alpha fusion (SEQ ID NO:48 &49) under the control of a CMV promoter.
- b) The human p85alpha gene (GenBank Accession number: M61906) was amplified using PCR according to standard protocols with primers p85-top-N (SEQ ID NO:20) and p85-bottom/-stop (SEQ ID NO:21). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produced a p85alpha-EGFP fusion (SEQ ID NO:66 &67) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. CHO expressing the human insulin receptor, in which the EGFP-p85 probe and/or the p85-EGFP probe may change its cellular distribution from cytoplasmic to membrane-associated within minutes in response to activation of the receptor with insulin.

Example 16:

Probes for detection of protein-tyrosine phosphatase redistribution.

- Useful for monitoring signalling pathways involving tyrosine kinases, e.g. to identify compounds which modulate the activity of the pathway in living cells.
 - Protein-tyrosine phosphatase1C, a tyrosine-specific phosphatase, is an inhibitory component in signalling pathways involving e.g. some growth factors.
- a) The human protein-tyrosine phosphatase 1C gene (GenBank Accession number: X62055) is amplified using PCR according to standard protocols with primers PTP-top (SEQ ID NO:99) and PTP-bottom/+stop (SEQ ID NO:101). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and EcoR1. This produces an EGFP-PTP fusion (SEQ ID NO:116 &117) under the control of a CMV promoter.

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b) The human protein-tyrosine phosphatase 1C gene (GenBank Accession number: X62055) is amplified using PCR according to standard protocols with primers PTP-top (SEQ ID NO:99) and PTP-bottom/-stop (SEQ ID NO:100). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and EcoR1. This produces a PTP-EGFP

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The resulting plasmids are transfected into a suitable cell line, e.g. MCF-7 in which the EGFP-PTP probe and/or the PTP-EGFP probe should change its cellular distribution from cytoplasm to the plasma membrane within minutes in response to activation of the growth inhibitory signalling pathway with e.g. somatostatin.

fusion (SEQ ID NO:118 &119) under the control of a CMV promoter.

Example 17:

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Probes for detection of Smad4 redistribution.

Useful for monitoring signalling pathways involving most members of the transforming growth factor-beta family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Smad4, a signal transducer, is a common component of signalling pathways induced by various members of the TGFbeta family of cytokines.

- 20 a) The human Smad4 gene (GenBank Accession number: U44378) was amplified using PCR according to standard protocols with primers Smad4-top and Smad4-bottom/+stop (SEQ ID NO:35). The PCR product was digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produce an EGFP-Smad4 fusion (SEQ ID NO:52 &53) under the control of a CMV promoter.
 - b) The human Smad4 gene (GenBank Accession number: U44378) was amplified using PCR according to standard protocols with primers Smad4-top (SEQ ID NO:33) and Smad4-bottom/-stop (SEQ ID NO:34). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produced a Smad4-EGFP fusion (SEQ ID NO:76 &77) under the control of a CMV promoter.

The resulting plasmids are transfected into a cell line, e.g. HEK293 in which the EGFP-Smad4 probe and/or the Smad4-EGFP probe should change its cellular distribution within minutes from cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. TGFbeta.

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Example 18:

Probes for detection of Stat5 redistribution.

Useful for monitoring signalling pathways involving the activation of tyrosine kinases of the Jak family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Stat5, signal transducer and activator of transcription, is a component of signalling pathways which are induced by e.g. many cytokines and growth factors.

- a) The human Stat5 gene (GenBank Accession number: L41142) was amplified using PCR according to standard protocols with primers Stat5-top (SEQ ID NO:30) and Stat5-bottom/+stop (SEQ ID NO:32). The PCR product was digested with restriction enzymes Bgl2 and Acc65I, and ligated into pEGFP-C1 (Clontech; Palo Alto; GenBank Accession number U55763) digested with Bgl2 and Acc65I. This produced an EGFP-Stat5 fusion (SEQ ID NO:54 &55) under the control of a CMV promoter.
- b) The human Stat5 gene (GenBank Accession number: L41142) was amplified using PCR according to standard protocols with primers Stat5-top (SEQ ID NO:30) and Stat5-bottom/stop (SEQ ID NO:331). The PCR product was digested with restriction enzymes Bgl2 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Bgl2 and Acc65I. This produced a Stat5-EGFP fusion (SEQ ID NO:78
 879) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. MIN6 in which the EGFP-Stat5 probe and/or the Stat5-EGFP probe should change its cellular distribution from cyto-plasmic to nuclear within minutes in response to activation signalling pathway with e.g. prolactin.

Example 19:

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Probes for detection of NFAT redistribution.

Useful for monitoring signalling pathways involving activation of NFAT, e.g. to identify compounds which modulate the activity of the pathway in living cells.

- NFAT, an activator of transcription, is a component of signalling pathways which is involved in e.g. immune responses.
 - a) The human NFAT1 gene (GenBank Accession number: U43342) is amplified using PCR according to standard protocols with primers NFAT-top (SEQ ID NO:84) and NFAT-bottom/+stop (SEQ ID NO:86). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and EcoR1. This produces an EGFP-NFAT fusion (SEQ ID NO:130 &131) under the control of a CMV promoter.
- b) The human NFAT gene (GenBank Accession number: U43342) is amplified using PCR according to standard protocols with primers NFAT-top (SEQ ID NO:84) and NFAT-bottom/stop (SEQ ID NO:85). The PCR product is digested with restriction enzymes Xho1 and E-coR1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and EcoR1. This produces an NFAT-EGFP fusion (SEQ ID NO:132 &133) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-NFAT probe and/or the NFAT-EGFP probe should change its cellular distribution from cytoplasmic to nuclear within minutes in response to activation of the signalling pathway with e.g. antibodies to CD3epsilon.

25 Example 20:

Probes for detection of NFkappaB redistribution.

Useful for monitoring signalling pathways leading to activation of NFkappaB, e.g. to identify compounds which modulate the activity of the pathway in living cells.

NFkappaB, an activator of transcription, is a component of signalling pathways which are responsive to a varity of inducers including cytokines, lymphokines, some immunosuppressive agents.

- a) The human NFkappaB p65 subunit gene (GenBank Accession number: M62399) is amplified using PCR according to standard protocols with primers NFkappaB-top (SEQ ID NO:87) and NFkappaB-bottom/+stop (SEQ ID NO:89). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-NFkappaB fusion (SEQ ID NO:142 & 143) under the control of a CMV promoter.
 - b) The human NFkappaB p65 subunit gene (GenBank Accession number: M62399) is amplified using PCR according to standard protocols with primers NFkappaB-top (SEQ ID NO:87) and NFkappaB-bottom/-stop (SEQ ID NO:88). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces an NFkappaB-EGFP fusion (SEQ ID NO:140 & 141) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-NFkappaB probe and/or the NFkappaB-EGFP probe should change its cellular distribution from cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. TNFalpha.

Example 21:

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Probe for detection of RhoA redistribution.

Useful for monitoring signalling pathways involving RhoA, e.g. to identify compounds which modulate the activity of the pathway in living cells.

RhoA, a small GTPase, is a component of many signalling pathways, e.g. LPA induced cytoskeletal rearrangements.

The human RhoA gene (GenBank Accession number: L25080) was amplified using PCR according to standard protocols with primers RhoA-top (SEQ ID NO:92) and RhoA-bottom/+stop (SEQ ID NO:93). The PCR product was digested with restriction enzymes

Hind3 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Hind3and BamH1. This produced an EGFP-RhoA fusion (SEQ ID NO:126 &127) under the control of a CMV promoter.

The resulting plasmid is transfected into a suitable cell line, e.g. Swiss3T3, in which the

EGFP-RhoA probe should change its cellular distribution from a reasonably homogenous to
a peripheral distribution within minutes of activation of the signalling pathway with e.g. LPA.

Example 22:

Probes for detection of PKB redistribution.

Useful for monitoring signalling pathways involving PKB e.g. to identify compounds which modulate the activity of the pathway in living cells.

PKB, a serine/threonine kinase, is a component in various signalling pathways, many of which are activated by growth factors.

- a) The human PKB gene (GenBank Accession number: M63167) is amplified using PCR according to standard protocols with primers PKB-top (SEQ ID NO:36) and PKB-bottom/+stop (SEQ ID NO:80). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-PKB fusion (SEQ ID NO:138 & 139) under the control of a CMV promoter.
- b) The human PKB gene (GenBank Accession number: M63167) was amplified using PCR according to standard protocols with primers PKB-top (SEQ ID NO:36) and PKB-bottom/stop (SEQ ID NO:37). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a PKB-EGFP fusion (SEQ ID NO:70 &71) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. CHO expressing the human insulin receptor, in which the EGFP-PKB probe and/or the PKB-EGFP probe cycles between cytoplasmic and membrane locations during the activation-deactivation process following addition of insulin. The transition should be apparent within minutes.

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SEQUENCE LISTING

5	(1) GENERAL INFORMATION
	(i) APPLICANT: NovoNordisk, BioImage
10	(ii) TITLE OF THE INVENTION: A Method of Detecting Cellular Translocation of Biologically Active Polypeptides Using Fluorescense Imaging
	(iii) NUMBER OF SEQUENCES: 143
15	(iv) CORRESPONDENCE ADDRESS:(A) ADDRESSEE: NovoNordisk, BioImage(B) STREET: Mørkhøjbygade 28(C) CITY: Søborg
20	(D) STATE: DK (E) COUNTRY: DENMARK (F) ZIP: 2860
	(v) COMPUTER READABLE FORM: (A) MEDIUM TYPE: Diskette
25	(B) COMPUTER: IBM Compatible (C) OPERATING SYSTEM: DOS (D) SOFTWARE: FastSEQ for Windows Version 2.0
30	(viii) ATTORNEY/AGENT INFORMATION: (A) NAME: , PV&P R
,	(B) REGISTRATION NUMBER: (C) REFERENCE/DOCKET NUMBER:
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	(D) TOPOLOGY: linear
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20	(2) INFORMATION FOR SEQ ID NO:17:	
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs	
25	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	,2, 20002002.	
30	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:	
	GTCTCGAGCC ATCATGAGCA GAAGCAAG	28
	(2) INFORMATION FOR SEQ ID NO:18:	
35	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs	
	(B) TYPE: nucleic acid (C) STRANDEDNESS: single	
40	(D) TOPOLOGY: linear	·
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:	
45	GTGGATCCCA CTGCTGCACC TGTGCTA	27
	(2) INFORMATION FOR SEQ ID NO:19:	
50	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs	
; -	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
55		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:	

	GTGGATCCTC ACTGCTGCAC CTGTGCTA		28
_	(2) INFORMATION FOR SEQ ID NO:20:		
5	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 40 base pairs		
•	(B) TYPE: nucleic acid		•
10	<pre>(C) STRANDEDNESS: single (D) TOPOLOGY: linear</pre>		
	(b) 101020011 111041		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:		
15	CGCGAATTCC GCCACCATGA GTGCTGAGGG GTACCAGTAC		40
	(2) INFORMATION FOR SEQ ID NO:21:		
	(i) SEQUENCE CHARACTERISTICS:		
20	(A) LENGTH: 32 base pairs		
	(B) TYPE: nucleic acid		
	(C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear		
25	·		
20	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:		
	CGCGGATCCT GTCGCCTCTG CTGTGCATAT AC		32
30	(2) INFORMATION FOR SEQ ID NO:22:		
	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 30 base pairs		
	(B) TYPE: nucleic acid		
35	<pre>(C) STRANDEDNESS: single (D) TOPOLOGY: linear</pre>		
	(D) TOPOLOGY: Tinear		
	(vi) ORIGINAL SOURCE:		
	(A) ORGANISM: p85-top-C		
40		•	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:	•	
	GGGAGATCTA TGAGTGCTGA GGGGTACCAG	·	30
45	(2) INFORMATION FOR SEQ ID NO:23:		
	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 34 base pairs(B) TYPE: nucleic acid		
50	(C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear		
	() CHONDING DESCRIPTION OF THE NO.		
55	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:		
JJ	GGGCGGATCC TCATCGCCTC TGCTGTGCAT ATAC		34
		•	e

	(2) INFORMATION FOR SEQ ID NO:24:		
	(i) SEQUENCE CHARACTERISTICS:		
5	(A) LENGTH: 33 base pairs		
J	(B) TYPE: nucleic acid		
		•	
	(C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear		
10			
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:		
	GTGAATTCGA CCATGTCGTC CATCTTGCCA TTC		33
	GIGARITOR CORTGICUTE CATCHIGGOR ITC	•	33
15	(2) INFORMATION FOR SEQ ID NO:25:		
15	(2) INFORMATION FOR SEQ ID NO:25:		
	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 31 base pairs	•	•
	(B) TYPE: nucleic acid		
20	·		
20	<pre>(C) STRANDEDNESS: single (D) TOPOLOGY: linear</pre>		
	(D) TOPOLOGI: Timear	·,	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:		
25	(XI) SEQUENCE DESCRIPTION: SEQ ID NO.23.		
20	GTGGTACCCA TGACATGCTT GAGCAACGCA C		31
	GIGGIACCCA IGACAIGCII GAGCAACGCA C		31
	(2) INFORMATION FOR SEQ ID NO:26:		
	(2) INFORMATION FOR SEQ ID NO.20.		
30	(i) SEQUENCE CHARACTERISTICS:	•	
30	(A) LENGTH: 32 base pairs		
	(B) TYPE: nucleic acid		
	(C) STRANDEDNESS: single		•
	(D) TOPOLOGY: linear		
35	(b) Torobodi: Timear		
33			
	(xi) SEQUENCE DESCRIPTION: SEO ID NO:26:		
	(AI) DEGUMENT DEDCATITION. DEG ID NOTED.		
	GTGGTACCTT ATGACATGCT TGAGCAACGC AC		32
40			
	(2) INFORMATION FOR SEQ ID NO:27:		
	(1)		
	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 31 base pairs		
45	(B) TYPE: nucleic acid		
٠.	(C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear		
	(2) 10101011 1111011		
50 .	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:		
•			
	GTGAATTCGT CAATGGAGCT GGAAAACATC G		31
		·	
	(2) INFORMATION FOR SEQ ID NO:28:		
55			
	(i) SEQUENCE CHARACTERISTICS:		
	· · · · · · · · · · · · · · · · · · ·		63

	(A) LENGTH: 30 base pairs		
	(B) TYPE: nucleic acid		
	(C) STRANDEDNESS: single		
5	(D) TOPOLOGY: linear		
Ð			
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:		
	(MIL) BEGOLMED BEBOKIFITON: BEQ ID NO:28:		
	GTGGATCCCT GCTGCTTCCG GTGGAGTTCG	3(n
10		5.	o .
	(2) INFORMATION FOR SEQ ID NO:29:		
	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 31 base pairs		
15	(B) TYPE: nucleic acid		
	(C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear		
,			
20	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:		
	The transfer of the transfer o		
	GTGGATCCCT AGCTGCTTCC GGTGGAGTTC G	3:	1
			-
	(2) INFORMATION FOR SEQ ID NO:30:	•	
25			
	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 32 base pairs		
	(B) TYPE: nucleic acid		
30	<pre>(C) STRANDEDNESS: single (D) TOPOLOGY: linear</pre>		
50	(D) TOPOLOGI: TIMEAR		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:		
	•		
35	GTAGATCTAC CATGGCGGGC TGGATCCAGG CC	32	2
		•	
	(2) INFORMATION FOR SEQ ID NO:31:		
	(i) CEOURNEE CHARACTERISE		
40	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 31 base pairs		
70	(B) TYPE: nucleic acid		
	(C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear	•	
	(2) 10104011 111142	,	
45		·	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:		
	GTGGTACCCA TGAGAGGGAG CCTCTGGCAG A	3:	1
50	(2) INDODUMENTON DOD OF THE PROPERTY.		
JU	(2) INFORMATION FOR SEQ ID NO:32:		
	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 31 base pairs		
	(B) TYPE: nucleic acid		
55	(C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear	•	
	,		64
			

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:	
5	GTGGTACCTC ATGAGAGGGA GCCTCTGGCA G	31
	(2) INFORMATION FOR SEQ ID NO:33:	
10	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 33 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
15	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:	
	GTGAATTCAA CCATGGACAA TATGTCTATT ACG	33
20	(2) INFORMATION FOR SEQ ID NO:34:	
25	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
30	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34: GTGGATCCCA GTCTAAAGGT TGTGGGTCTG C	31
	(2) INFORMATION FOR SEQ ID NO:35:	
35	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
40	(with CECUTARY DESCRIPTION OF THE SE	
45	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35: GTGGATCCTC AGTCTAAAGG TTGTGGGTCT GC	32
	(2) INFORMATION FOR SEQ ID NO:36:	
50	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
55	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:	

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	GTCT	'CGA	GGC 2	ACCA:	PGAG	CG A	CGTGC	3C									27
			(2)	INI (FORM	OITA	1 FOR	R SEC	OID	NO:3	7:						
5	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 27 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear																
10			(D)	TOP	Juog.		mear	-								•	
	•	(၁	ci) s	SEQUI	ENCE	DES	CRIPT	rion:	: SEÇ) ID	NO:3	37:					
15	TGGG	ATC	CGA (GCC	GTGC:	rg c	rggc	CG									27
13			(2)	INI	FORM	OITA	1 FOR	R SEC	Q ID	ио: 3	8:						•
20	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 1896 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear																
25				OLEC FEATU	CULE JRE:	TYPI	E: cI	AMC									
30		(2)	(B) (D)	LOC	ME/KI CATIO HER I	ON: :	li	1891 ION:			NO : 3	88:					
35														CCC Pro			48
														GTG Val 30			96
40														AAG Lys			144
45														GTG Val			192
50														CAC His			240
55														GTC Val			288

					TTC Phe												336
5	GTG	AAG	TTC	GAG	GGC	GAC	ACC	CTG	GTG	AAC	CGC	ATC	GAG	CTG	AAG	GGC	384
	Val	Lys	Phe 115	Glu	Gly	Asp	Thr	Leu 120	Val	Asn	Arg	Ile	Glu 125	Leu	Lys	Gly	
10					GAG Glu												432
10	116	130	PIIC	пуъ	Giu	wah	135	ASII	116	neu.	.GIY	140	пуъ	пеп	GIU	ıyı	
					CAC His												480
15	145					150					155					160	-
					AAC Asn 165												528
20		~~ ~	cmc	999		a. a		<i>a</i> . <i>a</i>	~			000	200		G3.G	000	F76
					GAC Asp												576
25					ccc												624
	Pro	Val	Leu 195	Leu	Pro	Asp	Asn	His 200	Tyr	Leu	Ser	Thr	Gln 205	Ser	Ala	Leu	
••		-			AAC												672
30	ser	. Lys 210	Asp	PIO	Asn	GIU	шуs 215	Arg	Asp	HIS	мес	220	ren	Leu	GIU	Pne	
					GGG												720
35	225	1111	HIG	AIa	Gly	230	1111	neu	GIY	Met	235	Giu	neu	TYL	пув	240	
					CGA Arg											_	768
40				•	245	,				250					255		
					GGC												816
•	Ala	Ala	GIN	260	Gly	GIY	GIY	GIĀ	265	Pro	Arg	Arg	THE	270	GIY	Val	
45					CCG												864
	Gly	Pro	275	vaı	Pro	GIÀ	Glu	Val 280		Met	Val	гÀг	285		Pro	Pne	
50					CGC Arg											GCG	912
50	nap	290	GIY	.10	arg	TYL	295	3111	neu	3111	1 1 7 1	300		- J. U	. Oly	.11.0	
																GTG Val	960
55	305		1.16.	val	SET	310		TÄL	мар	uis	315		nys	TIIL	AT 9	320	

										-							
		u 1.	ic ii	/S 11)	32	.e se :5	r Pr	o Pn	e Gl	u Hi 33	s Gl	n Th	т Ту	r Cyi	33	_	1008
5			o Al	34	.u 11	e Gī	n 11:	e re	u Lei 34!	u Ar	g Pho	e Aro	g His	350	Ası	r GTC n Val	1056
10		- 01	35	5	g As	р тт	e Lei	360	g Ala	a Se	r Thi	r Leı	365	Ala	Met	G AGA : Arg	1104
15	,,,,,	37	0	r 11	e va	I GII	375	Let 5	ı Met	Glu	1 Thi	380 380	Leu	Tyr	Lys	TTG Leu	1152
20	385		J 56.	L GI,	i GII	390	ser	Asn	Asp) His	395	: Cys	Tyr	Phe	Leu	TAC Tyr 400	1200
0.5	0111		C De	a Ari	405	, rec	гьуs	Tyr	lle	His 410	Ser	Ala	Asn	Val	Leu 415		1248
25	••••	Lot	, ner	420)	ser	Asn	Leu	Leu 425	Ser	Asn	Thr	Thr	Cys 430	Asp		1296
30		116	435	, ASL) Pne	GIY	Leu	A1a 440	Arg	Ile	Ala	GAT Asp	Pro 445	Glu	His	Asp	1344
35		450	Gly	PHE	neu	inr	455	Tyr	Val	Ala	Thr	CGC Arg 460	Trp	Tyr	Arg	Ala	1392
40	465	Olu	116	Met	ьeu	470	ser	ГÀЗ	Gly	Tyr	Thr 475	AAG Lys	Ser	Ile	Asp	Ile 480	1440
		DCI	Val	GIY	485	116	тел	Ala	Glu	Met 490	Leu	TCT Ser	Asn	Arg	Pro 495	Ile	1488
45	1110	rio	GIY	500	HIS	Tyr	Leu	Asp	Gln 505	Leu	Asn	CAC His	Ile	Leu 510	Gly	Ile	1536
50	CTG Leu	GGC Gly	TCC Ser 515	CCA Pro	TCC Ser	CAG Gln	GIU	GAC Asp 520	CTG Leu	AAT Asn	TGT Cys		ATC I Ile I	AAC . Asn	ATG Met	AAG Lys	1584
55	GCC Ala	CGA Arg 530	AAC Asn	TAC Tyr	CTA Leu	GIN.	TCT Ser 535	CTG Leu	CCC Pro	TCC Ser	Lys	ACC I Thr : 540	AAG (Lys \	GTG (Val)	GCT Ala	TGG Trp	1632

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										69		•					
								GAC Asp									1680
5								AAT Asn									1728
10								CAG Gln									1776
15								TTC Phe 600				Leu				/	1824
20								ATC Ile									1872
		GGA Gly						CTAG									1896
25	25 (2) INFORMATION FOR SEQ ID NO:39:																
30	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 631 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 															· .	
35	(ii) MOLECULE TYPE: protein(v) FRAGMENT TYPE: internal(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:																
40	Met 1												Val	Pro	Ile 15	Leu	
				20		_			25		_			30		Gly Ile	,
45		50					55			_		60				Thr	
	65		_	_	Phe	70	_			Pro	75		_		Gln	Lys 80 Glu	
50				100				_	105		_			110		Glu	
55		Asp	115				Gly	120				His	125			Gly Tyr	
		130					135					140					^

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	Asn 145	Tyr	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	Asp	Lys	Gln	Lys	Asn 160
	Gly	Ile	Lys	Val	Asn 165	Phe	Lys	Ile	Arg	His 170	Asn	Ile	Glu	Asp	Gly 175	Ser
5	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly
	Pro	Val	Leu 195	Leu	Pro	Asp	Asn	His 200	Tyr		Ser	Thr	Gln 205	Ser	Ala	Leu
10	Ser	Lys 210	Asp	Pro	Asn	Glu	Lys 215	Arg	qsA	His	Met	Val 220	Leu	Leu	Glu	Phe
	Val 225	Thr	Ala	Ala	Gly	Ile 230	Thr	Leu	Gly	Met	Asp 235	Glu	Leu	Tyr	Lys	Ser 240
	Gly	Leu	Arg	Ser	Arg 245	Ala	Gln	Ala	Ser	Asn 250	Ser	Thr	Met	Ala	Ala 255	Ala
15		•		260	Gly			_	265			_		270		
	_		275		Pro			280				_	285			
20		290			Arg		295					300				
	305				Ser	310					315					320
0.5			_	_	Ile 325		•			330			-	_	335	
25				340	Ile				345					350		
		_	355		Asp Val			360					365			7
30	-	370	_		Gln		375					380		_	_	
	385	_			Gly	390			_		395		_			400
35					405 Pro			_		410					415	
		-		420	Phe				425					430		
			435		Leu			440	_				445			
40		450			Leu		455					460				
	465				Cys	470		_	_	•	475	_			_	4.80
45	Phe	Pro	Gly	Lys	485 His	Tyr	Leu	Asp	Gln	490 Leu	Asn	His	Ile	Leu	495 Gly	Ile
	Leu	Gly	Ser	500 Pro	Ser	Gln	Glu	Asp	505 Leu	Asn	Cys	Ile	Ile	510 Asn	Met	Lys
	Ala	Arg	515 Asn	Tyr	Leu	Gln	Ser	520 Leu	Pro	Ser	Lys	Thr	525 Lys	Val	Ala	Trp
50	Ala	530 Lys	Leu	Phe	Pro	Lys	535 Ser	Asp	Ser	Lys	Ala	540 Leu	Asp	Leu	Leu	Asp
	545 Arg	Met	Leu	Thr	Phe	550 Asn	Pro	Asn	Lys	Arg	555 Ile	Thr	Val	Glu	Glu	560 Ala
55	Leu	Ala	His	Pro	565 Tyr	Leu	Glu	Gln	Tyr	570 Tyr	Asp	Pro	Thr	Asp	575 Glu	Pro
				580					585					590		

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	Val	Ala	Glu 595	Glu	Pro	Phe	Thr	Phe 600	Ala	Met	Glu		Asp 605	Asp	Leu	Pro	
	Lys	Glu 610		Leu	Lys		Leu 615		Phe	Gln				Arg	Phe	Gln	
5	Pro 625	Gly	Val	Leu	Glu	Ala 630	Pro										
			(2)	INF	ORMA	TION	FOR	SEÇ] ID	NO : 4	0:						
10		(i	(A) (B) (C)	EQUEN LENG TYPE STRA	TH: : nu ANDEI	1818 clei NESS	bas c ac	e pa id ngle	irs								
15			li) N	OLEC	CULE						τ						
20	•		(B)	NAN LOC OTI	CATIC	N: 1]	815	equen	ice							
		()	ci) S	EQUE	ENCE	DESC	RIP	: NOI	SEC	D	NO:4	10:					
25		GTG Val															48
30		GAG Glu															96
35		GGC Gly															144
40		ACC Thr 50															192
40		ACC Thr															240
45		CAC His															288
50		ACC Thr															336
55		AAG Lys														GGC Gly	384

		GAC Asp 130											432
5 .		TAC Tyr				Val							480
10		ATC Ile											528
15	GTG Val	CAG Gln											576
		GTG Val											624
20		AAA Lys 210											672
25		ACC Thr											720
30		CTC Leu										_	768
35		ATG Met											816
40		TCG Ser		Gly	Glu	Gly	Tyr	Gly	Met	Val	Ser		864
40		AAT Asn 290											912
45		CAC His											960
50		CGC Arg											1008
55		CCA Pro						Val				Asp	1056

						, 5				
					CTC Leu 360					1104
5					TAT Tyr					1152
10			Asn		CAC His				CTC Leu 400	1200
15					CTC Leu					1248
20	 				GAT Asp					1296
20	 				GCT Ala 440					1344
25					ATT Ile					1392
30					ATC Ile					1440
35					ATT Ile					1488
10					Lys					1536
40					TGG Trp 520					1584
45					GAT Asp					1632
50					GCT Ala				CAG Gln 560	1680
55				_	CCC Pro				Phe	1728

										14							
														GAA Glu 590			1776
5		GAA Glu												TAA			1818
10	•		(2)	INE	FORM	TION	1 FOF	SE(Q ID	NO:4	11:						
15		i)	(A) (B) (C)	EQUEN LENG TYPE STRA	TH: E: an ANDEI	605 mino ONESS	amir acio S: si	no ao 1 ingle	cids								
20				OLEC RAGMI			_										
20		(2	ci) S	EQUI	ENCE	DESC	CRIP	rion	: SE(QI Q	NO:4	11:					
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu	
25	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly	
	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile	
30	Сув	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr	
	Leu 65	Thr	Tyr	Gly	Val	Gln 70	Cys	Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys 80	
	Gln	His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu	
35	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu	
	Val	Lys			_	_				Asn	• -			Leu	Lys	Gly	
40	Ile	Asp 130	Phe	Lys	Glu	Asp	Gly 135	Asn	Ile	Leu	Gly	His 140	Lys	Leu	Glu	Tyr	
	Asn 145	_	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	Asp	Lys	Gln	Lys	Asn 160	
٠	Gly	Ile	Lys	Val	Asn 165		Lys	Ile	Arg	His 170	Asn	Ile	Glu	Asp	Gly 175	Ser	
45	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190		Gly	
	Pro	Val	Leu 195	Leu	Pro	Asp	Asn	His 200		Leu	Ser	Thr	Gln 205		Ala	Leu	
50	Ser	Lys 210	-	Pro	Asn	Glu	Lys 215		Asp	His	Met	Val 220		Leu	Glu	Phe	
	Val	Thr	Ala	Ala	Gly	Ile	Thr	Leu	Gly	Met	Asp	Glu	Leu	Tyr	Lys	Ser	
	225					230					235					240	
	_				245					250					255		
55	Glu	Met	Val	Arg	_	Gln	Val	Phe	Asp		Gly	Pro	Arg	Tyr		Asn	

265

```
Leu Ser Tyr Ile Gly Glu Gly Ala Tyr Gly Met Val Cys Ser Ala Tyr
                                  280
     Asp Asn Leu Asn Lys Val Arg Val Ala Ile Lys Lys Ile Ser Pro Phe
                              295
                                                  300
5
     Glu His Gln Thr Tyr Cys Gln Arg Thr Leu Arg Glu Ile Lys Ile Leu
                         310
                                              315
     Leu Arg Phe Arg His Glu Asn Ile Ile Gly Ile Asn Asp Ile Ile Arg
                      325
                                          330
     Ala Pro Thr Ile Glu Gln Met Lys Asp Val Tyr Ile Val Gln Asp Leu
10
                                      345
     Met Glu Thr Asp Leu Tyr Lys Leu Leu Lys Thr Gln His Leu Ser Asn
     Asp His Ile Cys Tyr Phe Leu Tyr Gln Ile Leu Arg Gly Leu Lys Tyr
                              375
15
     Ile His Ser Ala Asn Val Leu His Arg Asp Leu Lys Pro Ser Asn Leu
                          390
                                              395
     Leu Leu Asn Thr Thr Cys Asp Leu Lys Ile Cys Asp Phe Gly Leu Ala
                      405
                                          410
     Arg Val Ala Asp Pro Asp His Asp His Thr Gly Phe Leu Thr Glu Tyr
20
                                      425
     Val Ala Thr Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Ser Lys
                                  440
     Gly Tyr Thr Lys Ser Ile Asp Ile Trp Ser Val Gly Cys Ile Leu Ala
                              455
                                                  460
25
     Glu Met Leu Ser Asn Arg Pro Ile Phe Pro Gly Lys His Tyr Leu Asp
                          470
                                              475
      Gln Leu Asn His Ile Leu Gly Ile Leu Gly Ser Pro Ser Gln Glu Asp
                      485
                                          490
      Leu Asn Cys Ile Ile Asn Leu Lys Ala Arg Asn Tyr Leu Leu Ser Leu
30
                  500
                                      505
      Pro His Lys Asn Lys Val Pro Trp Asn Arg Leu Phe Pro Asn Ala Asp
                                  520
      Ser Lys Ala Leu Asp Leu Leu Asp Lys Met Leu Thr Phe Asn Pro His
                              535
                                                  540
35
      Lys Arg Ile Glu Val Glu Gln Ala Leu Ala His Pro Tyr Leu Glu Gln
                          550
                                              555
      Tyr Tyr Asp Pro Ser Asp Glu Pro Ile Ala Glu Ala Pro Phe Lys Phe
                      565
                                          570
      Asp Met Glu Leu Asp Asp Leu Pro Lys Glu Lys Leu Lys Glu Leu Ile
40
                                      585
      Phe Glu Glu Thr Ala Arg Phe Gln Pro Gly Tyr Arg Ser
              595
                                  600
```

(2) INFORMATION FOR SEQ ID NO:42:

45

50

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2529 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:

55 (A) NAME/KEY

- (A) NAME/KEY: Coding Sequence
- (B) LOCATION: 1...2526

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

5		GTG Val									CTG Leu	48
10		GAG Glu										96
15		GGC Gly										144
20		ACC Thr 50										192
20		ACC Thr										240
25		CAC His										288
30		ACC Thr								_	_	336
35		AAG Lys										384
40	_	GAC Asp 130										432
		TAC Tyr										480
45		ATC Ile					Asn					528
50		CAG Gln										576
55		GTG Val				Tyr			Ser			624

WO 98/45704 PCT/DK98/00145

		CCC Pro												672
5		GCC Ala												720
10		TCT Ser												768
15		GCC Ala 260											GGA Gly	816
		AAA Lys												. 864
20		AGC Ser												912
25		TTA Leu			Lys									960
30		GAA Glu												1008
35		GCA Ala 340												1056
40		GAA Glu		Met	Thr	Lys	Tyr	Leu	Thr	Lys				1104
40		CAA Gln												1152
45		AAG Lys												1200
50		TAC Tyr												1248
55		GAC Asp 420	Arg	Phe	Leu	Gln	Trp	Lys	Trp	Glu	Arg	Gln		1296

										-							
	GTG	ACC	AAA	AAC	ACT	TTC	AGG	CAG	TAT	CGA	GTG	CTA	GGA	AAA	GGG	GGC	1344
	Val	Thr	Lys	Asn	Thr	Phe	Arg	Gln	Tyr	Arg	Val	Leu	Gly	Lys	Gly	Gly	
			435				_	440	_	_			445				
5	TTC	GGG	GAG	GTC	TGT	GCC	TGC	CAG	GTT	CGG	GCC	ACG	GGT	AAA	ATG	TAT	1392
	Phe	Gly	Glu	Val	Cys	Ala	Cys	Gln	Val	Arg	Ala	Thr	Gly	Lys	Met	Tyr	
•		450				•	455					460					
	GCC	TGC	AAG	CGC	TTG	GAG	AAG	AAG	AGG	ATC	AAA	AAG	AGG	AAA	GGG	GAG	1440
10	Ala	Cys	Lys	Arg	Leu	Glu	Lys	Lys	Arg	Ile	Lys	Lys	Arg	Lys	Gly	Glu	•
	465					470					475					480	
	TCC	ATG	GCC	CTC	AAT	GAG	AAG	CAG	ATC	CTC	GAG	AAG	GTC	AAC	AGT	CAG	1488
	Ser	Met	Ala	Leu	Asn	Glu	Lys	Gln	Ile	Leu	Glu	Lys	Val	Asn	Ser	Gln	
15					485					490					495		
	TTT	GTG	GTC	AAC	CTG	GCC	TAT	GCC	TAC	GAG	ACC	AAG	GAT	GCA	CTG	TGC	1536
	Phe	Val	Val	Asn	Leu	Ala	Tyr	Ala	Tyr	Glu	Thr	Lys	Asp	Ala	Leu	Cys	
				500		•			505					510			
20																	
	TTG	GTC	CTG	ACC	ATC	ATG	TAA	GGG	GGT	GAC	CTG	AAG	TTC	CAC	ATC	TAC	1584
	Leu	Val	Leu	Thr	Ile	Met	Asn	Gly	Gly	Asp	Leu	Lys	Phe	His	Ile	Tyr	
			515					520					525				
25				AAC													1632
	Asn		Gly	Asn	Pro	Gly		Glu	Glu	Glu	Arg		Leu	Phe	Tyr	Ala	
		530					535					540				.*	
										~~~		~~~	~~~	220	3.00	CTC.	1600
00				CTC													1680
30		GIU	TTE	Leu	Cys	_	ьeu	GIU	Asp	Leu		Arg	GIU	ASII	Int	560	
	545					550					555					260	
	ma c	CCA	CAT	CTG	תתת	CCT	CAA	א א מ	አጥሮ	CTC	ጥጥአ	CAT	ርስጥ	ጥልጥ	GGC	CAC	1728
				Leu													1,20
35	ıyı	Arg	rap	Беа	565	FIO	GIU	ASII	110	570	DCu	vob	nop	-1-	575		
33					202					370							
	አጥጥ	» GG	ΔΤΟ	TCA	GAC	СТС	GGC	ጥጥር	GCT	стс	DAG	АТС	CCC	GAG	GGA	GAC	1776
				Ser													
	110	*** 3		580			~- <i>1</i>		585		J			590			
40				500					-								
40	CTG	ATC	CGC	GGC	CGG	GTG	GGC	ACT	GTT	GGC	TAC	ATG	GCC	CCC	GAA	GTC	1824
																Val	
	200		595	,	•9		1	600		1	-1-		605				
45	CTG	AAC	AAC	CAG	AGG	TAC	GGC	CTG	AGC	CCC	GAC	TAC	TGG	GGC	CTT	GGC	1872
,,,																Gly	
		610				- 4	615				•	620		-		-	
	TGC	CTC	ATC	TAT	GAG	ATG	ATC	GAG	GGC	CAG	TCG	CCG	TTC	CGC	GGC	CGT	1920
50																Arg	
	625			-		630			-		635			-		640	
	AAG	GAG	AAG	GTG	AAG	CGG	GAG	GAG	GTG	GAC	CGC	CGG	GTC	CTG	GÁC	ACG	1968
																Thr	
55	-		-	•	645					650					655		

	GAG Glu										2016
5	ATG Met										2064
10	GGG Gly 690										2112
15	AAG Lys										2160
20	CGC Arg										2208
20	GTG Val										2256
25	TTC Phe										2304
30	ACA Thr 770										2352
35	CCG Pro				•						2400
40	CTG Leu									Lys	2448
40	TCG Ser										2496
45	GTC Val		 	 			TAG				2529
50	(:	 INI EQUEI			-	NO:	43:				·

- (A) LENGTH: 842 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

# (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

	Met	Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Île	Leu
	1				5					10		<u>.</u>			15	_
10		Glu		20	_	-			25		_			30		
	Glu	Gly	Glu 35	Gly	qaA	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
15	Leu 65	Thr	Tyr	Gly	Val.	Gln 70	Сув	Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys 80
	Gln	His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu
20	_	Thr		100		_			105					110		
		Lys	115			_		120	•		_		125			
		Asp 130					135					140				
25	145	Tyr				150		_			155					160
	-	Ile	_		165		_			170					175	
30		Gln		180					185					190		
			195					200	_				205.			Leu
		Lys 210	-				215					220				
35	225					230					235					Ser 240
	-	Leu	_		245					250					255	
40				260					265	_				270		Gly
	_	_	275	-	_			280	_	_	_		285			Phe
45		290				_	295	_		_		300				Asp
45	305	_				310					315					Arg 320
					325					330					335	
50 .				340					345					350		Glu
	_		355					360					365			Val
E E		370					375	_				380				Lys
55	185		GIU	пÀг	PIO	390	ьys	GIU	ьeu	rne	395		сув	ATG	GIII	Ser 400

	Val	His	Glu	Tyr	Leu 405	Arg	Gly	Glu	Pro	Phe	His	Glu	Tyr	Leu	Asp 415	Ser
	Met	Phe	Phe	Asp 420	Arg	Phe	Leu	Gln	Trp 425		Trp	Leu	Glu	Arg		Pro
5	Val	Thr	Lys 435	Asn	Thr	Phe	Arg	Gln 440		Arg	Val	Leu	Gly 445		Gly	Gly
. ,	Phe	Gly 450	Glu	Val	Сув	Ala	Cys 455	Gln	Val	Arg		Thr 460	_	Lys	Met	Tyr
10	465				Leu	470					475				_	480
					Asn 485					490		_			495	
				500	Leu				505			_	_	510		-
15			515		Ile			520					525			_
		530			Pro		535					540			_	
20	545				Cys	550					555					560
					Lys 565		7			570		_	_	-	575	
05		*		580	Asp				585		-			590		_
25			595		Arg			600					605			
		610			Arg		615				_	620	_	_		_
30	625				Glu	630			_		635			_	_	640
					Lys 645					650					655	
35				660	Ser				665					670		_
33			675		Thr			680					685			
		690			Glu Glu		695					700				
40	705				Tyr	710					715					720
					725 Val					730					735	
45				740	Gly				745					750		
40			755					760					765			
		770			Phe		775					780				
50	785				Leu	790					795				_	800
					Arg 805					810					815	
55				820	Ser				825		HIS	nis	TIE	830	ser	ASN
JJ	uis		835	ser	Asn	SEL	ınr	61y 840	ser	ser						

WO 98/45704

		(2)	) INI	FORM	OITA	1 FOI	R SE	OID	NO:4	14:				
5	(:	(B)	LENG TYPI STRI	E: ni ANDEI	CHARA 1902 101e: ONESS Y: 1:	2 bas ic ac S: s:	se pa cid ingle	airs						
10		ii) 1 ix) 1			TYPI	E: cI	ANC							
15		(B)	) LO	CATION CATION	EY: ( ON: : INFOI	RMAT	1899 ION:	-						
	(:	xi) 8	SEQUI	ENCE	DES	CRIP:	LION	: SE(	Q ID	NO : 4	14:			
20	 GTG Val											 		48
25	GAG Glu													96
	 GGC Gly													144
30	ACC Thr 50													192
35	ACC Thr													240

288 CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 40 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 85 CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 45 100 105 110 GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 120 50 ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 135 130 55 AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 480 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn

								••							
	145				150				155				160		
5										ATC Ile				5:	28
10										CCC Pro				<b>5</b> '	76
10										ACC Thr				6:	24
15										GTC Val 220				. 6'	72
20										GAG Glu				7:	20
25										AGA Arg					6B
30										ACA Thr				8	16
30										GGA Gly					64
35										AAT Asn 300				و.	12
40		Leu								GCC Ala				9	60
45										AAA Lys				10	80
				Phe						GAA Glu		Gln		10	56
50			Val				Asp			CTT Leu	Gln			. 11	.04
55										CTI				11	.52

	370				375			380				
5			ATC Ile									1200
10			AGT Ser									1248
			GGT Gly 420								· .	1296
15			GTG Val								_	1344
20	 		AAG Lys									1392
25	 	-	GTT Val			 	 				_	1440
30			AAT Asn								_	1488
00	 		AAA Lys 500									1536
35	 		GCT Ala			 						1584
40			GAC Asp									1632
45			TCC Ser							Ile		1680
50			GCT Ala									1728
50			GAA Glu 580									1776
55			CAC His									1824

85 595 600 605 GTT ATG GAC TTG GAG GAG AGA ACC AAG AAT GGA GTT ATA CGG GGG CAG 1872 Val Met Asp Leu Glu Glu Arg Thr Lys Asn Gly Val Ile Arg Gly Gln 5 610 615 CCC TCT CCT TTA GCA CAG GTG CAG CAG TGA 1902 Pro Ser Pro Leu Ala Gln Val Gln Gln 10 (2) INFORMATION FOR SEQ ID NO:45: (i) SEQUENCE CHARACTERISTICS: 15 (A) LENGTH: 633 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 20 (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:45: Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 25 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 30 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 75 35 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 90 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 40 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 135 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 150 155 45 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 170 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 Pro Val Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 50 200 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 215 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 - 235 55 Gly Leu Arg Ser Arg Ala Arg Ala Ile Met Ser Arg Ser Lys Arg Asp

250

	Asn	Asn	Phe	Tyr 260	Ser	Val	Glu	Ile	Gly 265	Asp	Ser	Thr	Phe	Thr 270	Val	Leu
	Lys	Arg	Tyr 275	Gln	Asn	Leu	Lys	Pro 280	Ile	Gly	Ser	Gly	Ala 285	Gln	Gly	Ile
5	Val	Cys 290	Ala	Ala	Tyr	Asp	Ala 295	Ile	Leu	Glu	Arg	Asn 300	Val	Ala	Ile	Lys
٠	Lys 305	Leu	Ser	Arg	Pro	Phe 310	Gln	Asn	Gln		His 315	Ala	Lys	Arg	Ala	Туг 320
10		Glu	Leu		Leu 325		Lys	Суѕ	Val			Lys	Asn	Ile	Ile 335	
	Leu	Leu	Asn			Thr	Pro	Gln	Lys 345		Leu	Glu	Glu	Phe 350		Asp
•	Val	Tyr	Ile 355		Met	Glu	Leu	Met 360		Ala	Asn	Leu	Cys 365	Gln	Val	Ile
15	Gln	Met 370		Leu	Asp	His	Glu 375		Met	Ser	Tyr	Leu 380		Tyr	Gln	Met
	Leu 385	Cys	Gly	Ile	Lys	His 390		His	Ser	Ala	Gly 395		Ile	His	Arg	Asp
20			Pro	Ser	Asn 405		Val	Val	Lys	Ser 410		Cys	Thr	Leu	Lys 415	
	Leu	Asp	Phe	Gly 420	Leu	Ala	Arg	Thr	Ala 425	Gly	Thr	Ser	Phe	Met 430	Met	Thr
	Pro	Tyr	Val 435		Thr	Arg	Tyr	Tyr 440		Ala	Pro	Glu	Val 445	Ile	Leu	Gly
25	Met	Gly 450		Lys	Glu	Asn	Val 455	Asp	Leu	Trp	Ser	Val 460	Gly	Cys	Ile	Met
٠	Gly 465	Glu	Met	Val	Cys	His 470	Lys	Ile	Leu	Phe	Pro 475	Gly	Arg	Asp		11e
30	Asp	Gln	Trp	Asn	Lys 485	Val	Ile	Glu	Gln	Leu 490		Thr	Pro	Cys	Pro 495	Glu
	Phe	Met	Lys	Lys 500	Leu	Gln	Pro	Thr	Val 505	Arg	Thr	Tyr	Val	Glu 510	Asn	Arg
	Pro	Lys	Tyr 515	Ala	Gly	Tyr	Ser	Phe 520	Glu	Lys	Leu	Phe	Pro 525	Asp	Val	Lev
35	Phe	Pro 530	Ala	qaA.	Ser	Glu	His 535	Asn	Lys	Leu	Lys	Ala 540	Ser	Gln	Ala	Arg
	Asp 545	Leu	Leu	Ser	Lys	Met 550	Leu	Val	Ile	Asp	Ala 555	Ser	Lys	Arg	Ile	Ser 560
40	Val	Asp	Glu	Ala	Leu 565	Gln	His	Pro	Tyr	Ile 570	Asn	Val	Trp	Tyr	Asp 575	Pro
	Ser	Glu	Ala	Glu 580	Ala	Pro	Pro	Pro	Lys 585	Ile	Pro	Asp	Lys	Gln 590	Leu	Asp
	Glu	Arg	Glu 595	His	Thr	Ile	Glu	Glu 600	Trp	Lys	Glu	Leu	Ile 605	Tyr	Lys	Glu
45	Val	Met 610	Asp	Leu	Glu	Glu	Arg 615	Thr	Lys	Asn	Gly	Val 620	.Ile	Arg	Gly	Glr
	Pro 625	Ser	Pro	Leu		Gln 630	Val	Gln	Gln							

50 (2) INFORMATION FOR SEQ ID NO:46:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1824 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ix) FEATURE:

5 (A) NAME/KEY: Coding Sequence (B) LOCATION: 1...1821

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

40		( )	(i) S	EQUE	ENCE	DESC	RIPT	:NOI	SEÇ	) ID	NO: 4	6:				*	
10		ama	700	AAG	~~~	a	ana	OMO.	mm/C	700	ccc	CTC	CTC	ccc	አጥር	CTC	48
				Lys													40
		var	ser	гув	5 5	Giu	Giu	ьеu	PIIC	10	СТУ	vaı	Val	FIO	15	пец	
	1				5					10					1.0		
15	GTC.	GAG	СТС	GAC	GGC	GAC	GTA	ממכ	GGC	CAC	AAG	TTC	AGC	GTG	TCC	GGC	96
13				Asp								_		_		_	
	Val	OIU.	200	20	<b>U</b> -1				25		1 -			30		1	•
														-			
	GAG	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	AAG	CTG	ACC	CTG	AAG	TTC	ATC	144
20				Gly													
		•	35	-	-			40	-	-			45	_			
		•															
	TGC	ACC	ACC	GGC	AAG	CTG	CCC	GTG	CCC	TGG	CCC	ACC	CTC	GTG	ACC	ACC	192
	Cys	Thr	Thr	Gly	Lys	Leu	Pro	Val	Pro	Trp	Pro	Thr	Leu	Val	Thr	Thr	•
25		50					55					60					
				GGC													240
•		Thr	Tyr	Gly	Val		Суз	Phe	Ser	Arg	_	Pro	Asp	His	Met		
	65					70					75					80	•
30													<b></b>	ama	C3.C	ana	200
				TTC													288
	GIN	HIS	Авр	Phe		ьуs	ser	Ата	Met.		GIU	GIY	TÀT	vai	95	Giu	
•					85					90					95		
35	CGC	אככ	מידמ	TTC	ጥጥር	ΔΔG	GAC	GAC	GGC	ממכ	тъс	DAG	ACC	CGC	GCC	GAG	336
33				Phe											_		
	**** 9			100		-,-		<i>F</i>	105		- ]	-7-		110			
	GTG	AAG	TTC	GAG	GGC	GAC	ACC	CTG	GTG	AAC	CGC	ATC	GAG	CTG	AAG	GGC	384
40	Val	Lys	Phe	Glu	Gly	Asp	Thr	Leu	Val	Asn	Arg	Ile	Glu	Leu	Lys	Gly	
			115					120					125				
														*			
				AAG													432
	Ile	Asp	Phe	Lys	Glu	Asp	Gly	Asn	Ile	Leu	Gly	His	Lys	Leu	Glu	Tyr	
45		130					135					140					
																	400
				AGC													480
•		Tyr	Asn	Ser	His		Val	Tyr	Ile	Met			Lys	Gin	гуs		
	145					150					155					160	
50	-	5 m~	n n ~	~m~	7 7 C	ethini Ca	7 7 ~	7 mc	000	~~~	7 7 C	y m.c	G N C	CAC	ccc	<b>NGC</b>	528
				GTG													528
	GIY	тте	гÀ8	Val		rne	гуѕ	тте	arg			тте	GIU	ьвр	175	261	
					165					170					1/3		•
55	GTC.	CVG	רידירי	GCC	GAC	CAC	ጥልሮ	ראכ	כאכ	אמ	ארר	רכר	ልጥሮ	GGC	GAC	GGC	576
JJ																Gly	2.3
	val	0111	Leu	via	nap		- ] -	البدت	2111	וופת				1	P	1	

				180					185					190			
	CCC	GTG	CTG	CTG	CCC	GAC	AAC	CAC	TAC	CTG	AGC	ACC	CAG	TCC	GCC	CTG	624
												Thr					
5			195					200					205				
-												GTC					672
	Ser	-	qaA	Pro	Asn	GIu	_	Arg	Asp	His	Met	Val	Leu	Leu	Glu	Pne	•
10		210					215					220			•		
	GTG	ACC	GCC	GCC	GGG	ATC	AĊT	CTC	GGC	ATG	GAC	GAG	CTG	TAC	AAG	TCC	720
												Glu					
	225				-	230					235		•			240	
•																	
15												AGG					768
	Gly	Leu	Arg	Ser		GIA	гàа	Met	Ser	GIn 250	GIu	Arg	Pro	Thr	255	ıyr	
					245					230					255	٠	
	CGG	CAG	GAG	CTG	AAC	AAG	ACA	ATC	TĠĠ	GAG	GTG	CCC	GAG	CGT	TAC	CAG	816
20												Pro				_	
	_			260					265					270			
																	254
												TCT					864
25	Asn	Leu	275	Pro	vaı.	GIA	ser	280	Ala	ıyr	GIY	Ser	285	Cys	Ala	Ald	
25			2/5					250					205				
	TTT	GAC	ACA	AAA	ACG	GGG	TTA	CGT	GTG	GCA	GTG	AAG	AAG	CTC	TCC	AGA	912
	Phe	Asp	Thr	Lys	Thr	Gly	Leu	Arg	Val	Ala	Val	Lys	Lys	Leu	Ser	Arg	
		290					295					300					
30						> mm	a	~~~		202	* 66	m	202	<b>~</b>	CITIC	CCC	960
												TAC Tyr					960
	305	PIIC	Gin	Ber	110	310	1110	AIG	ם עם	A. 9	315	171	<b>A.</b> 9.	014	200	320	
	000																•
35												GGT					1008
	Leu	Leu	Lys	His	Met	Lys	His	Glu	Asn		Ile	Gly	Leu	Leu		Val	
					325					330					335		
	mmm	א כיא	CCT	CCA	N.C.C.	TOT	CTC	GNG	מאא	ጥጥር	ידיממ	GAT	GTG	ידי בידי	CTG	GTG	1056
40	-											Asp					1050
				340	5				345					350			
													•				•
												GTG					1104
	Thr	His		Met	Gly	Ala	Asp		Asn	Asn	Ile	Val		Cys	Gln	Lys	
45			355					360					365				
	CTT	מרמ	GAT	GAC	СДТ	GTT	CAG	ттс	СТТ	ATC	TAC	CAA	ATT	CTC	CGA	GGT	1152
																Gly	
		370	- 1-	<b>L</b> -			375		-		•	380			_	-	
50																	
												AGG					1200
		Lys	Tyr	Ile	His		Ala	Asp	Ile	Ile			Asp	Leu	гув	Pro 400	
	385					390					395					<b>400</b>	
<b>5</b> 5	AGT	ААТ	CTA	GCT	GTG	AAT	GAA	GAC	TGT	GAG	CTG	AAG	ATT	CTG	GAT	TTT	1248
																Phe	
	_							•	•			-			_		

					405					410					415			
5												GGC Gly					1296	
10												TGG Trp					1344	
10												ATG Met 460					1392	
15												ATT Ile					1440	
20												GAG Glu					1488	
25												TCT Ser					1536	
												GCC Ala					1584	
30												TCA Ser 540					1632	
35												GCT Ala					1680	
40	CCT Pro	GAT Asp	GAT Asp	GAA Glu	CCA Pro 565	GTG Val	GCC Ala	GAT Asp	CCT Pro	TAT Tyr 570	Asp	CAG Gln	TCC	TTT Phe	GAA Glu 575	AGC Ser	. 1728	
45					Ile					Ser		ACC Thr			Glu		1776	;
50				Val					Asp			A GAG		Glu		TGA	182	<u></u> 4
50																		

## (2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 607 amino acids
(B) TYPE: amino acid

90

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal

### (xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

		Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe		Gly	Val	Val	Pro		Leu
10	1				5		_		_	10			_		15	
•		Glu		20	_	-			25					30		
	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
15	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
	Leu 65	Thr	Tyr	Gly	Val	Gln 70	Cys	Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys 80
20	Gln	His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu
	Val	Lys	Phe 115	Glu	Gly	Asp	Thr	Leu 120	Val	Asn	Arg	Ile	Glu 125	Leu	Lys	Gly
25	Ile	Asp 130	Phe	Lys	Glu	Asp	Gly 135	Asn	Ile	Leu	Gly	His 140	Lys	Leu	Glu	Tyr
	Asn 145	Tyr	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	Asp	Lys	Gln	Lys	Asn 160
30		Ile	Lys	Val	Asn 165	Phe	Lys	Ile	Arg	His 170	Asn	Ile	Glu	Asp	Gly 175	Ser
	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	qaA	Gly
	Pro	Val	Leu 195	Leu	Pro	Asp	Asn	His 200	Tyr	Leu	Ser	Thr	Gln 205	Ser	Ala	Leu
35	Ser	Lys 210	Asp	Pro	Asn	Glu	Lys 215	Arg	Asp	His	Met	Val 220	Leu	Leu	Glu	Phe
	Val 225	Thr	Ala	Ala	Gly	Ile 230	Thr	Leu	Gly	Met	Asp 235	Glu	Leu	Tyr	Lys	Ser 240
40		Leu	Arg	Ser	Arg 245	Gly	Lys	Met	Ser	Gln 250		Arg	Pro	Thr	Phe 255	Tyr
	Arg	Gln	Glu	Leu 260	Asn	Lys	Thr	Ile	Trp 265	Glu	Val	Pro	Glu	Arg 270	Tyr	Gln
	Asn	Leu	Ser 275	Pro	Val	Gly	Ser	Gly 280	Ala	Tyr	Gly	Ser	Val 285	Cys	Ala	Ala
45	Phe	Asp 290	Thr	Lys	Thr	Gly	Leu 295	Arg	Val	Ala	Val	Lys 300	Lys	Leu	Ser	Arg
	Pro 305	Phe	Gln	Ser	Ile	Ile 310		Ala	Lys	Arg	Thr 315		Arg	Glu	Leu	Arg 320
50			Lys	His	Met 325		His	Glu	Asn	Val 330		Gly	Leu	Leu	Asp 335	Val
	Phe	Thr	Pro	Ala 340	Arg		Leu	Glu	Glu 345		Asn	Asp	Val	Tyr 350		Val
	Thr	His	Leu 355			Ala	Asp	Leu 360		Asn	Ile	Val	Lys 365		Gln	Lys
55	Leu	Thr 370		Asp	His	Val	Gln 375		Leu	Ile	Tyr	Gln 380		Leu	Arg	Gly

Ser Asn Leu Ala Val Asn Glu Asp Cys Glu Leu Lys Ile Leu Asp Phe 405 415 5 Gly Leu Ala Arg His Thr Asp Asp Glu Met Thr Gly Tyr Val Ala Thr 420 Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Trp Met His Tyr Asn 435 Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Trp Met His Tyr Asn 435 Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Trp Met His Tyr Asn 435 Gln Thr Val Asp Ile Trp Ser Val Gly Cys Ile Met Ala Glu Leu Leu 450 455 466 Thr Gly Arg Thr Leu Phe Pro Gly Thr Asp His Ile Asp Gln Leu Lys 465 470 Leu Ile Leu Arg Leu Val Gly Thr Pro Gly Ala Glu Leu Leu Lys 485 Leu Ile Leu Arg Leu Val Gly Thr Pro Gly Ala Glu Leu Leu Lys Lys 485 15 Ile Ser Ser Glu Ser Ala Arg Asn Tyr Ile Gln Ser Leu Thr Gln Met 500 501 502 Val Asp Leu Leu Glu Lys Met Leu Val Leu Asp Ser Asp Lys Arg Ile 500 510 510 Thr Ala Ala Gln Ala Leu Ala His Ala Tyr Phe Ala Gln Tyr His Asp 545 540 Thr Ala Ala Gln Ala Leu Ala His Ala Tyr Phe Ala Gln Tyr His Asp 545 Fro Asp Asp Glu Pro Val Ala Asp Pro Tyr Asp Gln Ser Phe Glu Ser 586 580 585 590 Ile Ser Phe Val Pro Pro Pro Leu Asp Gln Glu Glu Met Glu Ser 595 30 (2) INFORMATION FOR SEQ ID NO:48:  (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2907 base pairs (B) TypE: nucleic acid (C) STRANDENNESS: single (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: CDNA (ix) FEATURE:  (A) NAME/KEY: Coding Sequence (B) LOCATION: 12904 (D) OTHER INFORMATION:  45 GTC GAG CAG GAG GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro 11e Leu 1 5 GTC GAG CTG GAC GAC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro 11e Leu 1 5 GTC GAG CTG GAC GAC GAG GAG CTG TTC ACC GAG GTG ACC TTC CGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 GAG GAC GAG GAG GAG GAC CTA CC GAG CTG AAG CTG AAG TTC ATC Glu Gly Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile			Lys	Tyr	Ile	His	Ser	Ala	Asp	Ile	Ile		Arg	Asp	Leu	Lys		
405 410 415  Gly Leu Ala Arg His Thr Asp Asp Glu Met Thr Gly Tyr Val Ala Thr 420 425 430  Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Trp Met His Tyr Asn 435 440 445  Gln Thr Val Asp Ile Trp Ser Val Gly Cys Ile Met Ala Glu Leu Leu 450 Thr Gly Arg Thr Leu Phe Pro Gly Thr Asp His Ile Asp Gln Leu Lys 465 470  Leu Ile Leu Arg Leu Val Gly Thr Pro Gly Ala Glu Leu Leu Lys 485 490 495  15 Ile Ser Ser Glu Ser Ala Arg Asn Tyr Ile Gln Ser Leu Thr Gln Met 500 Pro Lys Met Asn Phe Ala Asn Val Phe Ile Gly Ala Asn Pro Leu Ala 515 520 525  Val Asp Leu Leu Glu Lys Met Leu Val Leu Asp Ser Asp Lys Arg Ile 500 515 520 525  Thr Ala Ala Gln Ala Leu Ala His Ala Tyr Phe Ala Gln Tyr His Asp 545 555 560 570 575  Arg Asp Leu Leu Ile Asp Glu Trp Lys Ser Leu Thr Tyr Asp Glu Val Ser 565 570 575  Arg Asp Leu Leu Ile Asp Glu Trp Lys Ser Leu Thr Tyr Asp Glu Val 580 11e Ser Phe Val Pro Pro Pro Leu Asp Gln Glu Glu Met Glu Ser 595 600 605  30 (2) INFORMATION FOR SEQ ID NO:48:  (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2907 base pairs (B) TYPE: nucleic acid (C) STRANBEENESS: single (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: cDNA (ix) FEATURE:  40  ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15  GTC GAG CTG GAC GGC GAG GTA AAC GGC CAC AAG TTC AGC GTG TCC GCC Val Glu Leu Asp Gly His Lys Phe Ser Val Ser Gly 20 55 GAG GGG GAG GGC GAT GCC CAC CTG CTG Val Glu Leu Asp Gly His Lys Phe Ser Val Ser Gly 20 55 GAG GGG GAG GGC GAT GCC ACC CTG CTG AAG CTG ACC CTG AAG TTC ACC CTG AAG CTG CTG CAC CTG Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 55 GAG GGG GAG GGC GAT GCC CAC CTG CTG CTG CTG CTG CTG CTG CTG CTG CT		385	2 - 2	7.00	7 J -	۲ <i>۲</i>		C1.,	Λαn	Cira	C1	395	T	т10	T 011	7.00	400 Dho	
Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Trp Met His Tyr Asn  Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Trp Met His Tyr Asn  435  440  61n Thr Val Asp Ile Trp Ser Val Gly Cys Ile Met Ala Glu Leu Leu  450  455  466  Thr Gly Arg Thr Leu Phe Pro Gly Thr Asp His Ile Asp Gln Leu Lys  465  Leu Ile Leu Arg Leu Val Gly Thr Pro Gly Ala Glu Leu Leu Lys Lys  485  490  495  15 Ile Ser Ser Glu Ser Ala Arg Asn Tyr Ile Gln Ser Leu Thr Gln Met  500  Pro Lys Met Asn Phe Ala Asn Val Phe Ile Gly Ala Asn Pro Leu Ala  515  520  731  Thr Ala Ala Gln Ala Leu Ala His Ala Tyr Phe Ala Gln Tyr His Asp  545  Thr Ala Ala Gln Ala Leu Ala His Ala Tyr Phe Ala Gln Tyr His Asp  545  556  Pro Asp Asp Glu Pro Val Ala Asp Pro Tyr Asp Gln Ser Phe Glu Ser  565  Arg Asp Leu Leu Ile Asp Glu Trp Lys Ser Leu Thr Tyr Asp Glu Val  580  11e Ser Phe Val Pro Pro Pro Leu Asp Gln Glu Glu Met Glu Ser  595  600  (2) INFORMATION FOR SEQ ID NO:48:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 2907 base pairs  (B) TYPE: nucleic acid  (C) STRANDEENDESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: cDNA  (ix) FEATURE:  (A) NAME/KEY: Coding Sequence  (B) LOCATION: 12904  (C) OTHER INFORMATION:  45  ATG GTG AGC AGG GGG GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG  Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu  1 5 10  GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC  Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly  20  55  GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC AGC  GAG GGC GAG GGC GAT GCC CAC CTG CTG CTG CAC CTG CAG GAG GTG CCC CTG CTG CALC CTG CTG CTG CALC CTG CTG CTG CTG CTG CTG CTG CTG CTG CT	_					405			_	_	410					415		
435	5	Gly	Leu	Ala	_	His	Thr	Asp	Asp		Met	Thr	Gly	Tyr		Ala	Thr	
10	•	Arg	Trp	-	Arg	Ala	Pro	Glu		Met	Leu	Asn	Trp		His	Tyr	Asn	
Thr Gly Arg Thr Leu Phe Pro Gly Thr Asp His Ile Asp Gln Leu Lys 465 465 465 465 465 465 465 465 465 465	10	Gln		Val	Asp	Ile	Trp		Val	Gly	Cys	Ile		Ala	Glu	Leu	Leu	
Leu Ile Leu Arg Leu Val Gly Thr Pro Gly Ala Glu Leu Leu Lys Lys 485 485 486 487 4886 4886 4886 4886 4886 4886 4			Gly	Arg	Thr	Leu		Pro	Gly	Thr	Asp		Ile	qaA	Gln	Leu		
15 Ile Ser Ser Glu Ser Ala Arg Asn Tyr Ile Gln Ser Leu Thr Gln Met 500  Pro Lys Met Asn Phe Ala Asn Val Phe Ile Gly Ala Asn Pro Leu Ala 515  520  Val Asp Leu Leu Glu Lys Met Leu Val Leu Asp Ser Asp Lys Arg Ile 530  Thr Ala Ala Gln Ala Leu Ala His Ala Tyr Phe Ala Gln Tyr His Asp 545  Fro Asp Asp Glu Pro Val Ala Asp Pro Tyr Asp Gln Ser Phe Glu Ser 565  Pro Asp Asp Glu Pro Val Ala Asp Pro Tyr Asp Gln Ser Phe Glu Ser 565  Arg Asp Leu Leu Ile Asp Glu Trp Lys Ser Leu Thr Tyr Asp Glu Val 580  Ser Ser Ser Ser Ser Leu Thr Tyr Asp Glu Val 580  Ser Ser Ser Ser Ser Leu Thr Tyr Asp Glu Val 580  Ser Ser Ser Ser Ser Ser Leu Thr Tyr Asp Glu Val 580  Ser Ser Ser Ser Ser Ser Ser Leu Thr Tyr Asp Glu Val 580  Ser Ser Ser Ser Ser Ser Leu Thr Tyr Asp Glu Val 580  Ser Ser Ser Ser Ser Ser Leu Thr Tyr Asp Glu Val 580  Ser Ser Ser Ser Ser Ser Ser Leu Thr Tyr Asp Glu Val 580  Ser Ser Ser Ser Ser Ser Ser Ser Leu Thr Tyr Asp Glu Val 580  Ser Ser Ser Ser Ser Ser Ser Ser Ser Leu Thr Tyr Asp Glu Val 580  Ser			Ile	Leu	Arg			Gly	Thr	Pro	_		Glu	Leu	Leu	-		
Pro Lys Met	15	Ile	Ser	Ser			Ala	Arg	Asn	_		Gln	Ser	Leu			Met	
Val Asp Leu Leu Glu Lys Met Leu Val Leu Asp Ser Asp Lys Arg Ile		Pro	Lys			Phe	Ala	Asn			Ile	Gly	Ala			Leu	Ala	
Thr Ala Ala Gln Ala Leu Ala His Ala Tyr Phe Ala Gln Tyr His Asp 545 550 555 555  Pro Asp Asp Glu Pro Val Ala Asp Pro Tyr Asp Gln Ser Phe Glu Ser 565 570 570  Arg Asp Leu Leu Ile Asp Glu Trp Lys Ser Leu Thr Tyr Asp Glu Val 580 1le Ser Phe Val Pro Pro Pro Leu Asp Gln Glu Glu Met Glu Ser 595 600 605  30 (2) INFORMATION FOR SEQ ID NO:48:  (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2907 base pairs (B) TYPE: nucleic acid 35 (C) STRANDEDNESS: single (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: cDNA (ix) FEATURE:  (A) NAME/KEY: Coding Sequence (B) LOCATION: 12904 (D) OTHER INFORMATION:  45 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:  ATG GTG AGC AAG GGC GAG GAG GTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15  GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30  55 GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC	00.	Val	_		Leu	Glu	Lys			Val	Leu	Asp			Lys	Arg	Ile	
Pro Asp Asp Glu Pro Val Ala Asp Pro Tyr Asp Gln Ser Phe Glu Ser 565 570 570 575  Arg Asp Leu Leu Ile Asp Glu Trp Lys Ser Leu Thr Tyr Asp Glu Val 580 580 585 600 585 600 585 600 605  Ile Ser Phe Val Pro Pro Pro Leu Asp Gln Glu Glu Met Glu Ser 595 600 600 605  30 (2) INFORMATION FOR SEQ ID NO:48:  (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2907 base pairs (B) TYPE: nucleic acid 35 (C) STRANDEDNESS: single (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: cDNA (ix) FEATURE:  (A) NAME/KEY: Coding Sequence (B) LOCATION: 12904 (D) OTHER INFORMATION:  45 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:  ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15  GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30  55 GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC	20			Ala	Gln	Ala			His	Ala	Tyr			Gln	Tyr	His	_	
25 Arg Asp Leu Leu Ile Asp Glu Trp Lys Ser Leu Thr Tyr Asp Glu Val 580  1le Ser Phe Val Pro Pro Pro Leu Asp Gln Glu Glu Met Glu Ser 595  30  (2) INFORMATION FOR SEQ ID NO:48:  (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2907 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: cDNA (ix) FEATURE:  (A) NAME/KEY: Coding Sequence (B) LOCATION: 12904 (D) OTHER INFORMATION:  45  ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10  GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25  GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC			Asp	Asp	Glu			Ala	Asp	Pro	_		Gln	Ser	Phe		•	•
Ile Ser Phe Val Pro Pro Leu Asp Gln Glu Glu Met Glu Ser 595 600 605  30 (2) INFORMATION FOR SEQ ID NO:48:  (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2907 base pairs (B) TYPE: nucleic acid  35 (C) STRANDEDNESS: single (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: cDNA (ix) FEATURE:  40  (A) NAME/KEY: Coding Sequence (B) LOCATION: 12904 (D) OTHER INFORMATION:  45 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:  ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15  GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30  55 GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC	25	Arg	Asp	Leu			Asp	Glu	Trp	-		Leu	Thr	туг			Val	
(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2907 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: cDNA (ix) FEATURE:  (A) NAME/KEY: Coding Sequence (B) LOCATION: 12904 (D) OTHER INFORMATION:  45  ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15  GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30  55  GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC		Ile	Ser			Pro	Pro	Pro			Gln	Glu	Glu			Ser		
(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2907 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: cDNA (ix) FEATURE:  (A) NAME/KEY: Coding Sequence (B) LOCATION: 12904 (D) OTHER INFORMATION:  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:  ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15  GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30  55 GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC			,	595					600					605				
(A) LENGTH: 2907 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: cDNA (ix) FEATURE:  (A) NAME/KEY: Coding Sequence (B) LOCATION: 12904 (D) OTHER INFORMATION:  (Xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:  ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15  GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30  55 GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC	30			(2)	) IN	FORM	OITA	V FO	R SE	Q ID	NO:	48:						
(C) STRANDEDNESS: single (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: cDNA (ix) FEATURE:  (A) NAME/KEY: Coding Sequence (B) LOCATION: 12904 (D) OTHER INFORMATION:  45  ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15  GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30  55  GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC		*	(:															4
(ii) MOLECULE TYPE: cDNA (ix) FEATURE:  (a) NAME/KEY: Coding Sequence (b) LOCATION: 12904 (D) OTHER INFORMATION:  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:  ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15  GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30  55 GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC				(B)	TYP	E: ni	ucle:	ic a	cid									
(ix) FEATURE:  (A) NAME/KEY: Coding Sequence (B) LOCATION: 12904 (D) OTHER INFORMATION:  45  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:  ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15  GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30  55  GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC	35								_	e								
(A) NAME/KEY: Coding Sequence (B) LOCATION: 12904 (D) OTHER INFORMATION:  45  ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15  GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30  55  GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC			(:	ii) 1	MOLE	CULE	TYP	E: c	AMC									
(B) LOCATION: 12904 (D) OTHER INFORMATION:  45  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:  ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15  GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30  55  GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC	40		(:	ix)	FEAT	JRE:												
(D) OTHER INFORMATION:  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:  ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15  GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30  55 GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC									_	eque	nce							
ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15  GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30  55 GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC																		
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 10 15  GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30  55 GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC	45		(:	xi) :	SEQUI	ENCE	DES	CRIP'	TION	: SE	Q ID	NO:	48:					
50  GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20  SGAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC	*																	48
GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30  55 GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC			Val	Ser	Lys	_	Glu	Glu	Leu	Phe		Gly	Val	Val	Pro		Leu	
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30  55 GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC	50																	
20 25 30  55 GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC																		96
					_	,	•	,	<b></b> -	-							-	
CIR OIL OIR OIL BOD WIFE THE TAT CIA TAD THER THE HER TAD LIFE TIC	55																	144

			35					40					45				•
5		ACC Thr 50															192
10		ACC Thr															240
		CAC His															288
15		ACC Thr				4											336
20		AAG Lys															384
25		GAC Asp 130															432
30	Asn 145		Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	Asp	Lys	Gln	ГÀв	Asn 160	480
		ATC Ile															528
35		CAG Gln															576
40		GTG Val															624
45		AAA Lys 210	Asp										Leu				672
50		ACC Thr										Glu					720
50		CTC Leu									Gln						768
55																GAC Asp	816

			260			a.	265				270		
5											TTC Phe		864
10											GGC Gly		912
10											GTA Val		960
15											CGG Arg		1008
20											GCA Ala 350		1056
25											TTT Phe		1104
											GCC Ala		1152
30											AGC Ser		1200
35											CCC Pro		1248
40											TTC Phe 430		1296
45			Asp				Val				GTT Val		1344
50		Ile				Glu				Glu		ATT	1392
50	Leu				Ile				Ile			TAT Tyr 480	1440
55												CAA Gln	1488

							94							
			485				490				495			-
5								CTC Leu					1530	6
10								TCT Ser					1584	4
10								ACT Thr 540					163	2
15								CCA Pro					168	0
20								TTA Leu					172	8
25								AAT Asn					177	6
30								GCG Ala					182	4
30								GGA Gly 620	Asn				187	2
35								TTC Phe					192	0.0
40								TAC Tyr					196	8
45								TTA Leu					201	16
						Val				Ile		GCT Ala	206	54
<b>50</b>					Tyr							AGT Ser	21:	12
55												GAA Glu	210	60

										90							•
	705					710					715					720	
5	ATC Ile	CAA Gln	ATG Met	AAA Lys	AGG Arg 725	ACA Thr	GCT Ala	ATT Ile	GAA Glu	GCA Ala 730	TTT Phe	AAT Asn	GAA Glu	ACC . Thr	ATA Ile 735	AAA Lys	2208
	ATA Ile	TTT Phe	GAA Glu	GAA Glu 740	CAG	TGC Cys	CAG Gln	ACC Thr	CAA Gln 745	GAG Glu	CGG Arg	TAC Tyr	AGC Ser	AAA Lys 750	GAA Glu	TAC Tyr	2256
10	ATA Ile	GAA Glu	AAG Lys 755	TTT Phe	AAA Lys	CGT Arg	GAA Glu	GGC Gly 760	AAT Asn	GAG Glu	AAA Lys	GAA Glu	ATA Ile 765	CAA Gln	AGG Arg	ATT Ile	2304
15	ATG Met	CAT His 770	AAT Asn	TAT Tyr	GAT Asp	AAG Lys	TTG Leu 775	AAG Lys	TCT Ser	CGA Arg	ATC Ile	AGT Ser 780	GAA Glu	ATT Ile	ATT Ile	GAC Asp	2352
20	AGT Ser 785	AGA Arg	AGA Arg	AGA Arg	TTG Leu	GAA Glu 790	GAA Glu	GAC Asp	TTG Leu	AAG Lys	AAG Lys 795	CAG Gln	GCA Ala	GCT Ala	GAĞ Glu	TAT Tyr 800	2400
25	CGA Arg	GAA Glu	ATT Ile	GAC Asp	AAA Lys 805	CGT Arg	ATG Met	AAC Asn	AGC Ser	ATT Ile 810	AAA Lys	CCA Pro	GAC Asp	CTT Leu	ATC Ile 815	CAG Gln	2448
	CTG Leu	AGA Arg	AAG Lys	ACG Thr 820	AGA Arg	GAC Asp	CAA Gln	TAC Tyr	TTG Leu 825	ATG Met	TGG Trp	TTG Leu	ACT Thr	CAA Gln 830	AAA Lys	GGT	2496
30	GTT Val	CGG	CAA Gln 835	AAG Lys	AAG Lys	TTG Leu	AAC Asn	GAG Glu 840	Trp	TTG Leu	GGC Gly	AAT Asn	GAA Glu 845	AAC Asn	ACT Thr	GAA Glu	2544
35	GAC Asp	CAA Gln 850	Tyr	TCA Ser	CTG Leu	GTG Val	GAA Glu 855	Asp	GAT Asp	GAA Glu	GAT Asp	TTG Leu 860	Pro	CAT His	CAT	GAT Asp	2592
40	GAG Glu 865	Lys	ACA Thr	TGG	AAT Asn	GTT Val 870	Gly	AGC Ser	AGC Ser	AAC	CGA Arg 875	Asn	AAA Lys	GCT Ala	GAA Glu	AAC Asn 880	2640
45	CTG Leu	TTG Leu	CGA Arg	GGG Gly	AAG Lys 885	Arg	GAT Jak	GGC Gly	ACT	TTI Phe	Lei	GTC Val	CGG Arg	GAG Glu	AG0 Se1 895	AGT Ser	2688
	AAA Lys	CAG Gln	GGC Gly	TGC Cys	Туг	GCC Ala	TGC Cys	TCT S Sei	T GTA Val	. Val	GT(	GAC L Asp	GGC Gly	GAA Glu 910	Va.	A AAG l Lys	2736
50	CAT His	TGI Cys	GTC Val	. Ile	AAC Asr	: AAA	A ACI	A GC c Ala 920	a Thi	GG(	TA'	r GG( r Gly	TT1 Phe 925	a Ala	GA(	g CCC u Pro	2784
55	TAT TYI	AAC Asr	TTC	TAC	AGC Ser	TC:	r CTO	G AA	A GAZ s Glu	A CTO	G GT	G CTA	A CAT	TAC	CA.	A CAC n His	2832

		930					935					940					•
5															GCC Ala	TAC Tyr 960	2880
		GTA Val							TGA						,	·	290
10	٠		(2)	INI	FORM	MOITA	ı FOI	R SE	) ID	NO:4	19:						
15		<b>()</b>	(B) (C)	LENC TYPI STRA	ETH: E: ar ANDEI	968 nino	amin acio 3: s:	no ao i ingle	cids								
20		(7	ii) f v) FI xi) S	MOLE(	CULE ENT	TYPI IYPE	E: p:	rote: tern	al	Q ID	NO:	49:					
25	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile 15	Leu	
		Glu	Leu	Asp 20		Asp	Val	Asn	Gly 25		Lys	Phe	Ser	Val 30	Ser	Gly	
30		_	35					40					45		Phe		
		50					55					60			Thr		
35	65					70					75				Met Gln	80	
30			_		85					90					95 Ala		
	_			100				Leu	105 Val				Glu	110 Leu			
40		130					135		Ile			140	1	Lev	Glu		
4.5	145					150					155					160	
45	-		_		165					170	l				Gly 175 Asp		
				180			•		185					190	)	Leu	
50		· Lys	195 Asp				Lys	200 Arg	١				205 Let	;		ı Phe	
	Val			Ala	Gly	Ile 230			Gly	Met	Asp 235	Glu		а Туг	r Lys	Ser 240	
55	Gly	Leu	Arg	Ser	Met 245		Ala	Glu	Gly	7 Tyr 250		туг	Arg	y Ala	255	ı Tyr	

	Asp	Tyr	Lys	Lys 260	Glu	Arg	Glu	Glu	Asp 265	Ile	Asp	Leu	His	Leu 270	Gly	Asp
	Ile	Leu	Thr 275	Val	Asn	Lys	Gly	Ser 280	Leu	Val	Ala	Leu	Gly 285	Phe	Ser	Asp
5	Gly	Gln 290	Glu	Ala	Arg	Pro	Glu 295	Glu	Ile	Gly	Trp	Leu 300	Asn	Gly	Tyr	Asn
	Glu 305	Thr	Thr	Gly	Glu	Arg 310	Gly	Asp	Phe	Pro	Gly 315		Tyr	Val	Glu	Tyr 320
10		Gly			325					330					335	
	Arg	Pro	Leu	Pro 340	Val	Ala	Pro	Gly	Ser 345	Ser	Lys	Thr	Glu	Ala 350	Asp	Val
		Gln	355					360	_				365			
15		Asp 370					375					380				
	385		_			390					395					400
20		Leu			405					410					415	
	. •	Leu		420					425					430		
	_	Leu	435					440					445			
25		Met 450	•				455					460				
	465	Leu		_	-	470					475					480
30	_	Leu		•	485		•			490					495	
		Ser		500					505					510		
		Pro	515					520					525			
35		Leu 530					535					540				
	545					550					555					560
40		Ala			565	•				570					575	
	_	Tyr 		580					585					590		
4=	· <del>-</del>	Thr	595				•	600					605			
45		Gly 610		-			615					620				
	625					630	_	_	_	_	635					64
50		Phe			645					650		·			655	
		Ala		660					665					670	ļ	
		Lys	675					680					685	i		
55	Val	Gly 690		Lys	Leu	His	Glu 695		Asn	Thr	Gln	Phe 700		GIU	гтув	se

	Arg	Glu	Tyr	Asp	Arg	Leu	Tyr	Glu	Glu	Tyr		Arg	Thr	Ser	Gln		
	705					710					715					720	
	Ile	Gln	Met	Lys	Arg 725	Thr	Ala	Ile	Glu	Ala 730	Phe	Asn	Glu	Thr	11e 735	Lys	
5	Ile	Phe	Glu	Glu 740		Сув	Gln	Thr	Gln 745	Glu	Arg	Tyr	Ser	Lys 750	Glu	Tyr	
•	Ile	Glu	Lys 755		Lys	Arg	Glu	Gly 760		Glu	Lys	Glu	Ile 765	Gln	Arg	Ile	
10	Met	His		Tyr	Asp	Lys	Leu 775		Ser	Arg	Ile	Ser 780	Glu	Ile	Ile	Asp	
10	.Ser		Arg	Arg	Leu	Glu 790		Asp	Leu	Lys	Lys 795	Gln		Ala	Glu	Tyr 800	
	Arg	Glu	Ile	Asp	Lys 805		Met	Asn	Ser	Ile 810		Pro	Asp	Leu	Ile 815		
15	Leu	Arg	Lys	Thr 820		Asp	Gln	Tyr	Leu 825		Trp	Leu	Thr	Gln 830	Lys	Gly	•
	Val	Arg	Gln 835		Lys	Leu	Asn	Glu 840		Leu	Gly	Asn	Glu 845	Asn	Thr	Glu	
20	Asp	Gln 850	Tyr	Ser	Leu	Val	Glu 855	Asp	Asp	Glu	Asp	Leu 860	Pro	His	His	Asp	
20	Glu 865	Lys		Trp	Asn	Val 870	Gly	Ser	Ser	Asn	Arg 875		Lys	Ala	Glu	Asn 880	
			Arg	Gly	Lys 885	Arg		Gly	Thr	Phe 890			Arg	Glu	Ser 895	Ser	
25	Lys	Gln	Gly	Cys 900	Tyr		Cys	Ser	Val 905		Val	Asp	Gly	Glu 910		Lys	• , •
	His	ĊĀB	Val 915	Ile		Lys	Thr	Ala 920	Thr		Tyr	Gly	Phe 925		Glu	Pro	
30	Tyr	Asn 930	Leu		Ser	Ser	Leu 935	Lys		Leu	Val	Leu 940		Tyr	Gln	His	
•	Thr 945	Ser		Val	Gln	His		Asp	Ser	Leu	Asn 955		Thr	Leu	Ala	Tyr 960	•
		Val	Tyr	Ala	Gln 965	Gln		Arg	ŗ								
35			(2	) IN			N FC	R SE	Q II	NO:	50:						
		(	-		NCE												
40		•	(A)	LEN	GTH:	216	0 ba	se r									
40			(C)	STR	ANDE	DNES	SS: S	ingl	e								
					CULE												
45					TURE:												
			(E	) LC	ME/H CATI THER	ON:	i	. 215	7	ence							
50		ı	(xi)	SEQU	JENCI	E DES	SCRII	PTIO	N: S	EQ II	ои с	:50:					
																C CTG	41
55	Met	c Va.	. Sei	с гу	5 5	ו האו	u GT	и пел	u PN	10	. 31	y va	. va	ı Pi	15	e Leu	

						33						
	GAG Glu											96
5	GGC Gly											144
10	ACC Thr 50											192
15	ACC Thr										AAG Lys 80	240
	CAC His											288
20	ACC Thr											336
25	AAG Lys											384
30	GAC Asp 130											432
35	TAC Tyr											480
40	ATC Ile											528
40			Asp							Asp	GGC Gly	576
45		Leu			Tyr				Ser		CTG Leu	624
50								Lev			TTC Phe	672
55	Thr			Thr			Glu				S TCC Ser 240	720

						100					
	CTC Leu									_	768
5	CCA Pro										816
10	 GCT Ala										864
15	GAA Glu 290										912
20	AAA Lys										960
20	 TGT Cys			-	-	-					1008
25	GGA Gly										1056
30	TAC Tyr										1104
35	TCC Ser 370										1152
40	TGG Trp										1200
	GAA Glu								Val		1248
45	CAC His										1296
50	CGA Arg										1344
55								Gly		CCA Pro	1392

	AGT Ser									1440
5	 GGA Gly									1488
10	CCA Pro							_	•	1536
15	GAT Asp								TCA Ser	1584
	GCA Ala 530								_	1632
20	CAG Gln									1680
25	AGG Arg									1728
30	GAA Glu									1776
35	GGT Gly									1824
	CAG Gln 610	Ser								1872
40	TGT Cys									1920
45	TTT Phe									1968
50	 TAT							_		2016
55	TGG Trp									2064

		ATT Ile 690															2112
5		ACT Thr														TAA	2160
10			(2)	INI	FORM	ATION	V FOI	R SE(	Q ID	NO:5	51:						
15		<b>i)</b>	(A) (B)	EQUEN LENC TYPI STRA	GTH: E: ar	719 nino	amin acid	no ad	cids	•							
	•		(D)	TOP	DLOG	7: 1i	inear	r									
20		. (1	/) FI	MOLE( RAGMI SEQUI	ENT T	TYPE:	int	erna	al	Q ID	NO:	51:					·
	Met	Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro		Leu	
25	1 Val	Glu	Leu	_	5 Gly	Asp	Val	Asn	_	10 His	Lys	Phe	Ser		15 Ser	Gly	•
	Glu	Gly		20 Gly	Asp	Ala	Thr	_	25 Gly	Lys	Leu	Thr		TAs	Phe	Ile	
00	Cys	Thr	35 Thr	Gly	ГÀЗ	Leu		40 Val	Pro	Trp	Pro		45 Leu	Val	Thr	Thr	
30		50 Thr	Tyr	Gly	Val		55 Cys	Phe	Ser	Arg	_	60 Pro	qaA	His	Met	Lys 80	
	65 Gln	His	Asp	Phe	Phe 85	70 Lys	Ser	Ala	Met	Pro 90	75 Glu	Gly	Tyr	Val	Gln 95		,
35	Arg	Thr	Ile	Phe		Lys	Asp	Asp	Gly 105		Tyr	Lys	Thr	Arg		Glu	
	Val	Lys	Phe		Gly	Asp	Thr	Leu 120		Asn	Arg	Ile	Glu 125		Lys	Gly	
40	Ile	Asp		Lys	Glu	Asp	Gly 135		Ile	Leu	Gly	His 140		Leu	Glu	Tyr	
40	Asn 145		Asn	Ser	His	Asn 150		Tyr	Ile	Met	Ala 155		Lys	Gln	Lys	Asn 160	
		Ile	Lys	Val	Asn 165		Lys	Ile	Arg	His 170		Ile	Glu	Asp	Gly 175	Ser	
45	Val	Gln	Leu	Ala 180		His	Tyr	Gln	Gln 185		Thr	Pro	Ile	Gly 190	Asp	Gly	
	Pro	Val	Leu 195		Pro	qaA	Asn	His 200	Tyr	Leu	Ser	Thr	Gln 205	Ser		Leu	
50	Ser	Lys 210		Pro	Asn	Glu	Lys 215	Arg		His	Met	Val 220	Leu		Glu	Phe	
	Val 225		Ala	Ala	Gly	Ile 230	Thr		Gly	Met	Asp 235	Glu		Tyr	Lys	Ser 240	
		Leu	Arg	Ser	Arg 245			Ala	Ser	Asn 250	Ser		Met	Ser	Ser 255	Ile	
55	Leu	Pro	Phe	Thr		Pro	Val	Val	Lys			Leu	Gly	Trp		Lys	

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	Ser	Ala	Gly 275	Gly	Ser	Gly	Gly	Ala 280	Gly	Gly	Gly	Glu	Gln 285	Asn	Gly	Gln
	Glu	Glu 290	Lys	Trp	Cys	Glu	Lys 295	Ala	Val	Lys	Ser	Leu 300	Val	Lys	Lys	Leu
5	Lys 305	Lys	Thr	Gly	Arg	Leu 310	Asp	Glu	Leu	Glu	Lys 315	Ala	Ile	Thr	Thr	Gln 320
· .	Asn	Сув	Asn	Thr	Lys 325	Cys	Val	Thr	Ile	Pro 330		Thr	Cys	Ser	Glu 335	Ile
10	Trp	Gly	Leu	Ser 340	Thr	Pro	Asn	Thr	Ile 345	Asp	Gln	Trp	Asp	Thr 350	Thr	Gly
	Leu	Tyr	Ser 355	Phe	Ser	Glu	Gln	Thr 360	Arg	Ser	Leu	Asp	Gly 365	Arg	Leu	Gln
	Val	Ser 370	His	Arg	Lys	Gly	Leu 375	Pro	His	Val	Ile	Tyr 380	Сув	Arg	Leu	Trp
15	385	_				390					395	_		Ile		400
	_		_		405			_	_	410			_	Val	415	
20	_			420					425					Val 430		
			435					440					445	Asp	_	_
	Thr	His 450	Ser	Ile	Pro	Glu	Asn 455	Thr	Asn	Phe	Pro	Ala 460	Gly	Ile	Glu	Pro
25	Gln 465	Ser	Asn	Tyr	Ile	Pro 470	Glu	Thr	Pro	Pro	Pro 475	Gly	Tyr	Ile	Ser	Glu 480
	Asp	Gly	Glu	Thr	Ser 485	Asp	Gln	Gln	Leu	Asn 490	Gln	Ser	Met	Ąsp	Thr 495	Gly
30	Ser	Pro	Ala	Glu 500	Leu	Ser	Pro	Thr	Thr 505	Leu	Ser	Pro	Val	Asn 510	His	Ser
			515					520					525	Trp		
		530					535		_		-	540		Phe		
35	Ser 545	Gln	Pro	Ser	Leu	Thr 550	Val	Asp	Gly	Phe	Thr 555	qaA	Pro	Ser	Asn	560
					565	•				570				Asn	575	
40				580					585		_			Leu 590		
		_	595					600	_			_	605	Ala		
		610					615					620		Pro		
45	625					630		•			635			Asn		640
					645					650				Phe	655	
50	Val	Tyr	Gin	ьеи 660	Tnr	Arg	Met	Cys	Thr 665	He	Arg	Met	ser	Phe 670	Vai	гÀŧ
	Gly	Trp	Gly 675	Ala	Glu	Tyr	Arg	Arg 680		Thr	Val	Thr	Ser 685	Thr	Pro	Cys
•	Trp	Ile 690	Glu	Leu	His	Leu	Asn 695	Gly	Pro	Leu	Gln	Trp 700		Asp	Lys	Va:
55	Leu		Gln	Met	Gly	Ser	Pro	Ser	Val	Arg	Cys	Ser	Ser	Met	Ser	

(2) INFORMATION	FOR	SEQ	ID	NO:52:
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		. (2	, 114.	FORM	HITOI	N FO	K SE	עד ל	NO::	5∠:						
5	(	(A) (B) (C)	LENG TYP: STR	NCE ( GTH: E: n ANDE OLOG	242: ucle: DNES	l basic as	se pa cid ingle	airs								·
10			MOLE FEAT	CULE URE:	TYPI	E: cl	DNA		•					•		
15		(B	) LO	ME/KI CATIO HER :	ON:	1:	2418	equei	nce	4						
	(:	xi) :	SEQU	ENCE	DESC	CRIP'	rion	: SE	Q ID	NO:	52:					
20													ATC Ile 15			48
25													TCC Ser			96
30													TTC Phe			144
30													ACC Thr		:	192
35	Thr												ATG Met		:	240
40													CAG Gln 95		· :	288
45													GCC Ala			336
50													AAG Lys			384
50													GAG Glu			432
55													AAG Lys			480

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							100						
	145				150			155			160		
5			GTG Val							Asp			528
10			GCC Ala 180									5	576
10			CTG Leu									•	524
15			CCC Pro									• (	572 [*]
20			GCC Ala										720
25			TCT Ser									•	768
30			ATT Ile 260										816
			AGT Ser										864
35			AGA Arg	-								;	912
40			TTG Leu										960
45			AAA Lys									1	800
50			GGT Gly 340								CTC Leu	. 1	056
00											TAT	. 1	104
55											CCA Pro	1	152

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		370	•		375			380			
5										GGA Gly	1200
10										GAA Glu 415	1248
	GTG Val									CAT His	1296
15										GAG Glu	1344
20										ACC Thr	1392
25										CCT Pro	1440
20										GCA Ala 495	1488
30										CCA Pro	1536
35										ACT Thr	1584
40										CAG Gln	1632
45										CAC His	1680
50										GAG Glu 575	1728
50										GAG Glu	1776
55										TAC Tyr	1824

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											•
		595			600			605		•	
5	 			 		 	 		TCC Ser		 1872
10									GGC Gly		1920
	 _					 	 		AGG Arg		 1968
15			Val						AGA Arg 670		2016
20									AGT Ser		2064
25						 	 		CAG Gln		 2112
30									GCC Ala		2160
									CCA Pro		2208
35									CGT Arg 750		2256
40									GAT Asp		2304
45									CAC His		2352
50									CCG Pro		2400
			TTA Leu 805	TGA							2421

(2) INFORMATION FOR SEQ ID NO:53:

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```
(i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 806 amino acids
              (B) TYPE: amino acid
5
              (C) STRANDEDNESS: single
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: protein
            (v) FRAGMENT TYPE: internal
10
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:
     Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
15
     Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
                                      25
      Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
      Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
20
      Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
                          70
      Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                                          90
25
      Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
                  100
                                      105
      Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
                                  120
      Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
30
                              135
      Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
                          150
                                              155
      Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                                          170
35
      Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
                                      185
      Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
                                  200
      Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
40
                              215
                                                   220
      Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
                          230
                                              235
      Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Asn Ser Thr Met Asp
                                          250
45
      Asn Met Ser Ile Thr Asn Thr Pro Thr Ser Asn Asp Ala Cys Leu Ser
                                      265
      Ile Val His Ser Leu Met Cys His Arg Gln Gly Glu Ser Glu Thr
              275
                                  280
      Phe Ala Lys Arg Ala Ile Glu Ser Leu Val Lys Lys Leu Lys Glu Lys
50
                              295
      Lys Asp Glu Leu Asp Ser Leu Ile Thr Ala Ile Thr Thr Asn Gly Ala
                          310
                                               315
      His Pro Ser Lys Cys Val Thr Ile Gln Arg Thr Leu Asp Gly Arg Leu
                      325
                                          330
```

Gln Val Ala Gly Arg Lys Gly Phe Pro His Val Ile Tyr Ala Arg Leu 340 345 350

	Trp	Arg	Trp 355	Pro	Asp	Leu	His	Lys 360	Asn	Glu	Leu	Lys	His 365	Val	Lys	Туг
	Cha	Gln 370	Tyr	Ala	Phe	Asp	Leu 375	Lys	Cys	Asp	Ser	Val 380	Cys	Val	Asn	Pro
5	Tyr 385	His	Tyr	Glu	Arg	Val 390	Val	Ser	Pro	Gly	Ile 395	Asp	Leu	Ser	Gly	Le:
	Thr	Leu	Gln	Ser	Asn 405	Ala	Pro	Ser	Ser	Met 410	Met	Val	ГÀЗ	Asp	Glu 415	Туг
10	Val	His	Asp	Phe 420	Glu	Gly	Gln	Pro	Ser 425	Leu	Ser	Thr	Glu	Gly 430	His	Ser
	Ile	Gln	Thr 435	Ile	Gln	His	Pro	Pro 440	Ser	Asn	Arg	Ala	Ser 445	Thr	Glu	Thi
	Tyr	Ser 450	Thr	Pro	Ala	Leu	Leu 455	Ala	Pro	Ser	Glu	Ser 460	Asn	Ala	Thr	Ser
15	465	Ala				470					475					480
		Ile		_	485					490					495	
20	_	Pro		500					505	_			_	510		
		Tyr	515					520		_		_	525	,-		
		Tyr 530					535					540				
25	545	Pro				550			_		555	-				560
		Leu			565					570					575	-
30	_	Сув		580	٠.	-			585	_				590		
	•	Lys	595				•	600					605			
35		Pro 610 Arg					615					620				
35	625	Gln				630				_	635					64(
		Asp			645					650					655	
40				660					665					670		
	_	Arg Lys	675					680		_		_	685			
45		690 Ala			_		695		_			700				
	705	Asn				710					715					72
		Leu			725					730	_			•	735	
50		Ile		740					745					750		
	_	Gln	755					760	_	_	_		765			
55		770 Ala					775					780				
55	785		neu	O 1 11	u_u	790		GIU	val	neu	705		MEC	FIO	TIE	SU.

## Asp Pro Gln Pro Leu Asp 805

5	(i)	(A) (B) (C) (D)	INF EQUEN LENG TYPE STRA TOPO MOLEC	ICE C TH: 1: nu NDEI DLOGY	HARA 3120 aclei ONESS	CTER bas c ac s: si	RISTI se pa cid ngle	CS:	NO:5	4:					
15		(B)	LOC OTF	CATIC	N: 3	3	3117	equer	ice						
	()	ci) S	EQUE	ENCE	DESC	RIP	CION:	SEC	Q ID	NO:	54:				
20													CCC Pro		. 48
25													GTG Val 30		96
30													AAG Lys		144
35													GTG Val		192
40													CAC His		240
													GTC Val		288
45														GAG Glu	336
50														GGC Gly	384
55		Phe					Asn					Lys		TAC Tyr	432

		TAC Tyr										80
5		ATC Ile									5	28
10		CAG Gln									5	76
15	-	GTG Val								CTG Leu		24
20		AAA Lys 210									. 6	72
		ACC Thr									7	20
25		CTC Leu									7	68
30		GAC Asp									. 8	16
35		GAG Glu									8	64
40		GCC Ala 290								_	9	12
40		CTG Leu									9	60
45		GGG Gly								_	10	800
50		CAG Gln							Val	CGC Arg	10	56
55										GCC	13	104

•											
								ATG Met			1152
5	 			Gln		 		CTG Leu			1200
10								CAG Gln			1248
15								CAG Gln 430			1296
20								GAG Glu			1344
	 <del></del>	-		 	 	 		CGT Arg			1392
25								CAC His			1440
30								GAT Asp		_	1488
35								GGC Gly 510			1536
40								AAG Lys			1584
40								GAG Glu			1632
45								CTG Leu			1680
50						Ala		ACC Thr			1728
55								CAG Gln 590	Thr	AAG Lys	1776

	 							GTG Val						1824
5	 				-	_		ACC Thr						1872
10	 							ACC Thr						1920
15								GAG Glu					ACC . Thr	1968
								TCA Ser 665					_	2016
20	 -		GGT					ACA Thr				ACA		2064
25		TCT						AGC Ser						2112
30	 							GTC Val						2160
35								TGG Trp						2208
								GAC Asp 745						2256
40								AAG Lys						2304
45		Thr					Val	TTC Phe			Lys		AAC Asn	2352
50	Ser			His		Glu				Leu			TGG Trp 800	2400
55					Glu				Trp				TGG Trp	2448

								117						
			GAC Asp 820											2496
5			GAT Asp											2544
10			CTC Leu											2592
15			GAA Glu	Ile										2640
		_	AAC Asn											2688
20			TCC Ser 900											2736
25			CCT Pro											2784
30			CTG Leu											2832
35			GTC Val											2880
40			ACG Thr											2928
40	CAG Gln		TAT Tyr 980											2976
45			GAA Glu			Leu				Asp				3024
50	Val		CTC Leu		Arg				Ser					3072
55			GCC Ala	Gly				Ala				Ser	TGA 1	3120

## (2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1039 amino acids

- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- 10 (ii) MOLECULE TYPE: protein

5

(v) FRAGMENT TYPE: internal

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

15	Met	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu
	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
20	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
	Leu 65	Thr	Tyr	Gly	Val	Gln 70	Cys	Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys 80
<b>25</b>	Gln	His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	qaA	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu
30	Val	Lys	Phe 115	Glu	Gly	Asp	Thr	Leu 120	Val	Asn	Arg	Ile	Glu 125	Leu	Lys	Gly
	Ile	Asp 130	Phe	Lys	Glu	Asp	Gly 135	Asn	Ile	Leu	Gly	His 140	Lys	Leu	Glu	Tyr
	Asn 145	Tyr	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	Asp	Lys	Gln	Lys	Asn 160
35	Gly	Ile	Lys	Val	Asn 165	Phe	Lys	Ile	Arg	His 170	Asn	Ile	Glu	Asp	Gly 175	Ser
	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly
40	Pro	Val	Leu 195	Leu	Pro	Asp	Asn	His 200	Tyr	Leu	Ser	Thr	Gln 205	Ser	Ala	Leu
	Ser	Lys 210	Asp	Pro	Asn	Glu	Lys 215	Arg	qaA	His	Met	Val 220	Leu	Leu	Glu	Phe
	Val 225	Thr	Ala	Ala	Gly	Ile 230	Thr	Leu	Gly	Met	Asp 235	Glu	Leu	Tyr	Lys	Ser 240
45	Gly	Leu	Arg	Ser	Thr 245	Met	Ala	Gly	Trp	Ile 250	Gln	Ala	Gln	Gln	Leu 255	Gln
	Gly	Asp	Ala	Leu 260	Arg	Gln	Met	Gln	Val 265	Leu	Tyr	Gly	Gln	His 270	Phe	Pro
50	Ile	Glu	Val 275	Arg	His	Tyr	Leu	Ala 280	Gln	Trp	Ile	Glu	Ser 285	Gln	Pro	Trp
	Asp	Ala 290	Ile	Asp	Leu	Asp	Asn 295	Pro	Gln	Asp	Arg	Ala 300	Gln	Ala	Thr	Gln
	Leu 305	Leu	Glu	Gly	Leu	Val 310	Gln	Glu	Leu	Gln	Lys 315	Lys	Ala	Glu	His	Gln 320
55	Val	Gly	Glu	Asp	Gly 325	Phe	Leu	Leu	Lys	Ile 330	Lys	Leu	Gly	His	Tyr 335	Ala

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	Thr	Gln	Leu	Gln 340	Lys	Thr	Tyr	Asp	Arg 345	Cys	Pro	Leu	Glu	Leu 350		Arg
			355					360					365	Arg		
5		370					375					380		Met		
	385					390					395			Leu		400
10		_			405			_	_	410				Gln	415	
	Phe			420					425	_				430		
			435					440					445	Glu		
15	•	450					455					460		Arg		
	465					470					475			His		480
20					485					490	•			Asp	495	
				500	_	_	_		505			_		Gly 510	-	
25			515					520					525	Lys		
25		530					535				_	540		Glu		
	545					550		_			555		+	Leu		<b>560</b>
30					565		_			570				Gln	575	
				580					585			_		590 Asn		_
35			595					600		_	_	_	605	Gln		
		610					615					620		Ser		
	625					630				_	635			Thr	-	640
40					645					650				Lys	655	
				660					665					670 Thr		
45			675					680				_	685	Phe		
		690					695	_				700		Ser		
	705					710		•	•		715			Ala		720
50					725				_	730				Pro	735	
				740					745	_				750 Ser		
55			755					760	_				765	Leu		
	4	0.00	. –	-									- 4 -			

```
Asn Ser Ser Ser His Leu Glu Asp Tyr Ser Gly Leu Ser Val Ser Trp
                          790
     Ser Gln Phe Asn Arg Glu Asn Leu Pro Gly Trp Asn Tyr Thr Phe Trp
                      805
                                          810
     Gln Trp Phe Asp Gly Val Met Glu Val Leu Lys Lys His His Lys Pro
5
                                      825
                  820
     His Trp Asn Asp Gly Ala Ile Leu Gly Phe Val Asn Lys Gln Gln Ala
             835
                                  840
     His Asp Leu Leu Ile Asn Lys Pro Asp Gly Thr Phe Leu Leu Arg Phe
10
                              855
      Ser Asp Ser Glu Ile Gly Gly Ile Thr Ile Ala Trp Lys Phe Asp Ser
                          870
                                              875
      Pro Glu Arg Asn Leu Trp Asn Leu Lys Pro Phe Thr Thr Arg Asp Phe
                      885
                                          890
15
      Ser Ile Arg Ser Leu Ala Asp Arg Leu Gly Asp Leu Ser Tyr Leu Ile
                  900
                                      905
      Tyr Val Phe Pro Asp Arg Pro Lys Asp Glu Val Phe Ser Lys Tyr Tyr
              915
                                  920
                                                      925
      Thr Pro Val Leu Ala Lys Ala Val Asp Gly Tyr Val Lys Pro Gln Ile
20
                              935
      Lys Gln Val Val Pro Glu Phe Val Asn Ala Ser Ala Asp Ala Gly Gly
                          950
      Ser Ser Ala Thr Tyr Met Asp Gln Ala Pro Ser Pro Ala Val Cys Pro
                      965
                                          970
25
      Gln Ala Pro Tyr Asn Met Tyr Pro Gln Asn Pro Asp His Val Leu Asp
                                      985
      Gln Asp Gly Glu Phe Asp Leu Asp Glu Thr Met Asp Val Ala Arg His
                               1000
      Val Glu Glu Leu Leu Arg Arg Pro Met Asp Ser Leu Asp Ser Arg Leu
30
                            1015
                                                 1020
      Ser Pro Pro Ala Gly Leu Phe Thr Ser Ala Arg Gly Ser Leu Ser
                         1030
                                             1035
               (2) INFORMATION FOR SEQ ID NO:56:
35
            (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 1875 base pairs
              (B) TYPE: nucleic acid
              (C) STRANDEDNESS: single
40
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: cDNA
            (ix) FEATURE:
45
               (A) NAME/KEY: Coding Sequence
               (B) LOCATION: 1...1872
               (D) OTHER INFORMATION:
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:
50
                                                                            48
      ATG GCG GCG GCG GCG GCT CCG GGG GGC GGG GGC GGG GAG CCC AGG
      Met Ala Ala Ala Ala Ala Pro Gly Gly Gly Gly Glu Pro Arg
55
      GGA ACT GCT GGG GTC GTC CCG GTG GTC CCC GGG GAG GTG GAG GTG GTG
                                                                            96
```

Gly Thr Ala Gly Val Val Pro Val Val Pro Gly Glu Val Glu Val Val

		20			25			30		
5									CAG Gln	144
10									CAC His	 192
									CAT His	240
15									CGA Arg 95	288
20	 			 		 	 		CCC Pro	 336
25									GAG Glu	384
30									CAC His	432
									CAC His	480
35									ATC Ile 175	528
40									ATT Ile	576
45								_	GCC Ala	624
50									TAC Tyr	672
									ATG Met	720
55									CTC	768

						115					
			245			250			255		
5	ATT Ile										816
40	 ATT Ile										864
10	AAG Lys 290									_	912
15	GAC Asp										960
20	GTA Val										1008
25	 ACA Thr										1056
	GAT Asp										1104
30	 GCC Ala 370										1152
35	 AAA Lys										1200
40	GAT Asp										1248
45	GGT Gly										1296
	GGG Gly										1344
50	GGT Gly 450									CAT His	1392
55										ACT	1440

										120						
	465					470					475				480	·
5						GAC Asp										1488
10						CTT Leu										1536
						AAC Asn										1584
15			_			TAC Tyr										1632
20						ATT Ile 550			-							1680
25						CAA Gln										1728
30						CAT His										1776
00						AGA Arg										1824
35						-									GAG T	1873
40	AA		(2)	) IN	FORM	ATIO	N FO	R SE	Q ID	NO:	57:					1875
45		(:	(A) (B) (C)	LENG TYPI STR	GTH: E: a: ANDE	CHAR 624 mino DNES Y: 1	amin acio S: s:	no a d ingl	cids		•					
50		(7	v) F	RAGM	ENT '	TYPE TYPE DES	: in	tern	al	Q ID	NO:	57:				
55	1	Ala	Ala	Ala	Ala 5	Ala Val	Ala	Pro	Gly	Gly 10	Gly	Gly		15		
																120

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•				20					25					30		
	Lys	Gly	Gln 35	Pro	Phe	Asp	Val	Glý 40	Pro	Arg	Tyr	Thr	Gln 45	Leu	Gln	Tyr
5	Ile	Gly 50	Glu	Gly	Ala	Tyr	Gly 55	Met	Val	Ser	Ser	Ala 60	Tyr	Asp	His	Val
•	Arg 65	Lys	Thr	Arg	Val	Ala 70	Ile	Lys	Lys	Ile	Ser 75	Pro	Phe	Glu	His	Gln 80
• .	Thr	Tyr	Сув	Gln	Arg 85	Thr	Leu	Arg	Glu	Ile 90	Gln	Ile	Leu	Leu	Arg 95	Phe
10	Arg	His	Glu	Asn 100	Val	Ile	Gly	Ile	Arg 105	Asp	Ile	Leu	Arg	Ala 110	Pro	Thr
	Leu	Glu	Ala 115	Met	Arg	Asp	Val	Tyr 120	Ile	Val	Gln	qaA	Leu 125	Met	Glu	Thr
15	_	Leu 130	Tyr	Lys	Leu	Leu	Lys 135	Ser	Gln	Gln	Leu	Ser 140	Asn	Asp	His	Ile
	Cys 145	Tyr	Phe	Leu	Tyr	Gln 150	Ile	Leu	Arg	Gly	Leu 155	Lys	Tyr	Ile	His	Ser 160
	Ala	Asn	Val	Leu	His 165	Arg	Asp	Leu	Lys	Pro 170	Ser	Asn	Leu	Leu	11e 175	Asn
20				180					185		_			190	Ile	
			195					200					205		Ala	
25	_	210					215					220	,		Tyr	
	225					230			_	_	235				Met	240
					245			•	_	250	_		_		Leu 255	
30				260			_		265					270	Asn	
			275		_		_	280	_				285		Ser	
35		290			_		295				_	300	_		Lys	
	305					310					315				Arg	320
					325					330	•				Tyr 335	
40				340					345					350	Met	
			355			<del>-</del>		360		_			365		Gln	
45	Thr	Ala 370	Arg	Phe	Gln	Pro	Gly 375	Ala	Pro	Glu	Gly	Pro 380	Gly	Arg	Ala	Met
	385	_				390			_		395				Val	400
	Leu	Asp	Gly	Asp	Val 405	Asņ	Gly	Gln	Lys	Phe 410	Ser	Val	Ser	Gly	Glu 415	Gly
50				420			_		425					430	Cys	
			435					440					445		Leu	
55	Tyr	Gly 450	Val	Gln	Сув	Phe	Ser 455	Arg	Tyr	Pro	Asp	His 460	Met	Lys	Gln	His
	<b>A</b>	Th	m1	T	O	7.7 -	30 - 4.	-	~ 7	~ 1	<b></b>		~ 7	~ ~ ~		mb -

	465					470					475					480	•
	Ile	Phe	Tyr	Lys	Asp 485	Asp	Gly	Asn	Tyr	Lys 490	Thr	Arg	Ala	Glu	Val 495	Lys	
5	Phe	Glu	Gly	Asp 500	Thr	Leu	Val	Asn	Arg 505	Ile	Glu	Leu	Lys	Gly 510	Ile	Asp	
٠.	Phe	Lys	Glu 515	Asp	Gly	Asn	Ile	Leu 520	Gly	His	Lys	Met	Glu 525	Tyr	Asn	Tyr	
	Asn	Ser 530	His	Asn	Val	Tyr	Ile 535	Met	Ala	Asp	Lys	Pro 540	Lys	Asn	Gly	Ile	
10	545					550					555				Val	560	
			_		565					570		_	_	_	Pro 575		
15				580			_		585					590	Ser		
	_	*	595		_	_	_	600					605		Val		
20	Ala	610	GIÀ	тте	Tnr	HIS	615	мет	Asp	GIU	ьeu	1yr 620	гÀг	Pro	Gln	GIU	
20			(2)	) IN	FORM	ATIO	N FO	R SE	Q ID	NO:	58:						
<b>25</b>			(A) (B) (C) (D)	EQUEI LENG TYPI STRA	E: ni ANDEI	181! ucle: ONES: Y: l:	5 bas ic ac S: s: inea:	se pa cid ingle r	airs								
30			ix) 1 (A)	MOLE FEAT ) NAI ) LO	JRE: ME/KI	EY: (	Codi	ng S	eque	nce							
35				OT													
00		(:	xi) \$	SEQU	ENCE	DES	CRIP'	TION	: SE	Q ID	NO:	58:					
40															CAG Gln 15		48
45															GAA Glu		96
40															GTT Val		144
50															TGT Cys		192
55															GAG Glu		240

	ATC Ile											288
5	GAT Asp											336
10	TTG Leu											384
15	CAG Gln 130											432
20	CGT Arg											480
25	AAG Lys											528
	CAT His											576
30	CCA Pro											624
35	TGG Trp 210											672
40	TTC	Gly	Lys	His	Leu	Asp	Gln	Leu	Asn			720
45	CTT Leu											768
	GCT Ala										_	816
50	AAC Asn											864
55	AAA Lys 290											912

5		CTG Leu									_	960
		ATT										1008
10	CCT	AAG Lys										1056
15		CCA Pro										1104
20		GGC Gly 370										1152
25		GGC Gly										1200
		GAT Asp										1248
30		AAG Lys										1296
35		GTG Val										1344
40		TTC Phe 450									_	1392
45		TTC										1440
40		GGC Gly										1488
50										Tyr	AAC Asn	1536
55			Val			Asp			Gly		AAG Lys	1584

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		AAC Asn 530															1632
5																	
		GAC Asp															1680
	545	vah	mis	ıyı	GIII	550	Vali	1111	PIO	110	555	-	Gly	FIO	Vai	560	
10		CCC															1728
	Leu	Pro	Asp	Asn	His 565	Tyr	Leu	Ser	Thr	Gln 570	Ser	Ala	Leu	Ser	Lys 575	Asp	
					505					3,0					3,3	4	
		AAC															1776
15	Pro	Asn	GIU	ьув 580	Arg	Asp	HIS	Met	585	Leu	ьеи	GIU	Pne	590	Tnr	Ala	
	GCC	GGG	ATC	ACT	CTC.	GGC	ATG	GAC	GAG	CTG	TAC	AA (	STAA				1815
20	Ala	Gly	Ile 595	Thr	Leu	.Gly	Met	Asp 600	Glu	Leu	Tyr	Lys					
•			. (0)				. =0										
			(2)	INI	ORM	ALTOI	N FOI	K SE(	Q ID	NO:	59:						
25		<b>(</b>	(A) (B) (C)	LENC TYPE STRA	ETH: E: ar ANDEI	CHARA 604 mino ONES	amin acio 3: s:	no ao i ingle	cids								
30			(D)	TOPO	)LOG	?: 1:	inea	r									
						TYPI TYPE	_										
35		()	ci) S	SEQUI	ENCE	DES	CRIP'	rion	: SE	) ID	NO:	59:					
00	Met 1	Ala	Ala	Ala	Ala 5	Ala	Ala	Gly	Pro	Glu 10	Met	Val	Arg	Gly	Gln 15	Val	
	Phe	Asp	Val	_	Pro	Arg	Tyr	Thr		Leu	Ser	Tyr	Ile		Glu	Gly	
40	Ala	туr	Gly 35	20 Met	Val	Cys	Ser	Ala 40	25 Tyr	Ąsp	Asn	Leu	Asn 45	Lys Lys	Val	Arg	
	Val	Ala 50		Lys	Lys	Ile	Ser		Phe	Glu	His	Gln 60		Tyr	Cys	Gln	
	Arg	Thr	Leu	Arg	Glu		Lys	Ile	Leu	Leu	Arg	Phe	Arg	His	Glu		
45	65 T30	Ile	Gly	Tle	) an	70	Tle	מוז	7 ~~	7 J =	75 Bro		τİρ	G) u	Gln	80 Met	
	116	116	GIY	116	85	waħ	116	116	ALG	90	PIO	1111	116	Giu	95	Mec	
	_	Asp		100				_	105				_	110	-		
50	Leu	Leu	Lys 115		Gln	His	Leu	Ser 120	Asn	Asp	His	Ile	Cys 125		Phe	Leu	
	Tyr	Gln 130	Ile	Leu	Arg	Gly	Leu 135	Lys	Tyr	Ile	His	Ser 140		Asn	Val	Leu	
		Arg	qaA	Leu	Lys		Ser	Asn	Leu	Leu			Thr	Thr	Cys	Asp	
55	145 Leu	Lys	Ile	Cvs	Asp	150 Phe	Glv	Leu	Ala	Ara	155 Val		Asp	Pro	Asp	160 His	
		-, -		-,-			1	u		3					1		

					165					170					175	
	Asp	His	Thr	Gly 180	Phe	Leu	Thr	Glu	Tyr 185	Val	Ala	Thr	Arg	Trp 190	Tyr	Arg
5	Ala	Pro	Glu 195	Ile	Met	Leu	Asn	Ser 200	Lys	Gly	Tyr	Thr	Lys 205	Ser	Ile	Asp
	Ile	Trp 210	Ser	Val	Gly	Cys	Ile 215	Leu	Ala	Glu	Met	Leu 220	Ser	Asn	Arg	Pro
	Ile 225	Phe	Pro	Gly	Lys	His 230	Tyr	Leu	Asp	Gln	Leu 235	Asn	His	Ile	Leu	Gly 240
10	Ile	Leu	Gly	Ser	Pro 245	Ser	Gln	Glu	Asp	Leu 250	Asn	Cys	Ile	Ile	Asn 255	Leu
	Lys	Ala	Arg	Asn 260	Tyr	Leu	Leu	Ser	Leu 265	Pro	His	Lys	Asn	Lys 270	Val	Pro
15			275					280	_				285	Asp		
	_	290					295					300		Val		
	305					310					315			Ser		320
20					325					330				Asp	335	
		-		340		_			.345					Ala 350		•
25			355					360					365	Met Val		
	-	370					375	_				380		Glu		
30	385					390			•		395			Cys		400
	-	_			405	-	_			410	_			Leu	415	
	_			420					425					430 Gln		
35	_		435					440			•		445	Arg		
	Phe	450 Phe	Lys	Asp	Asp	Gly	455 Asn	Tyr	Lys	Thr	Arg	460 Ala	Glu	Val	Lys	Phe
40	465 Glu	Gly	Asp	Thr		470 Val	Asn	Arg	Ile			Lys	Gly	Ile		480 Phe
	Lys	Glu	Asp		485 Asn	Ile	Leu	Gly		490 Lys		Glu	туr		495 Tyr	Asn
45	Ser	His		500 Val	Tyr	Ile	Met		505 Asp	Lys	Gln	Lys	Asn 525		Ile	Lys
45	Val	Asn 530	515 Phe	Lys	Ile	Arg	His 535	520 Asn	Ile	Glu	Asp	Gly 540			Gln	Leu
	Ala 545		His	Tyr	Gln	Gln 550	Asn	Thr	Pro	Ile	Gly 555		Gly	Pro	Val	Leu 560
50		Pro	Asp	Asn	His 565			Ser	Thr	Gln 570	Ser	Ala	Leu		Lys · 575	Asp
	Pro	Asn	Glu	Lys 580		Asp	His	Met	Val 585	Leu		Glu	Phe		Thr	Ala
55	Ala	Gly	Ile 595	Thr	Leu	Gly	Met	Asp 600	Glu		Tyr	ГÀв				

(2)	INFORMATION	FOR	SEQ	ID	NO:60:
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5	(:	(A) (B) (C) (D) (ii) M (x) H (A) (B)	LENC TYPE STRA TOPO MOLEC FEATU NAM LOC	ME/KE	2511 clei DNESS TYPE	bas c ac s: si near C: cI	e pa	irs	ıce					
15	. (2			HER I				SEC	) ID	NO : 6	50:			·
20	 			AAC Asn 5										48
25				GGA Gly										96
20				CCT Pro										144
30	 			TAC Tyr										192
35				CAG Gln										240
40				GAC Asp 85										288
45				AAA Lys										336
43				TTC Phe										384
50				CTC Leu									GCC Ala	432
55	Ala										Glu		GAA Glu 160	480

_								CAG Gln					528
5								CAG Gln					576
10								CAG Gln					624
15								AAG Lys 220					672
20								CAG Gln					720
25				Val				GCC Ala					768
25								GGG Gly					816
30								GAG Glu		Glu			864
35								GAA Glu 300					912
40								AAC Asn					960
AE								TTG Leu				Ile	1008
45			Leu				Val	ACT			Tyr	ATG Met	1056
50						Arg				Pro		TAC	1104
55		Leu			Tyr				Gly			CCG Pro	1152

5	CGC Arg												1200
	CTG Leu												1248
10	TCC Ser												1296
15	TGC												1344
20	AAC Asn 450												1392
25	GTT Val											_	1440
	CAG Gln												1488
30	TTC Phe												1536
35	GAG Glu												1584
40	AAT Asn 530			Pro	Asp								1632
45	CCC Pro								Lys				1680
	AAT Asn							Thr				His	1728
50	AAC Asn		His				Ser				Arg	GAT Asp	1776
55		Ala				Lys				. Phe		GGG Gly	1824

																	•
												GTA Val 620					1872
5																	7.000
												ACC					1920
•	Phe	Ser	Val	Ser	Gly		Gly	Glu	Gly	Asp		Thr	Tyr	GIÀ	Lys		
	625					630					635					640	
10												CCC					1968.
	Thr	Leu	Lys	Phe		Cys	Thr	Thr	GIY	-	Leu	Pro	Val	Pro		Pro	
					645					650					655		
						cmc.		m> ~	000	ama	G3 G	maa	mma	300	000	ma C	2016
4=												TGC					2016
15	Thr	Leu	vaı		Thr	Leu	Thr	Tyr	_	vai	GIN	Cys	Pne		Arg	TYL	
				660					665					670			
	000	C N C	CNC	איזייר	אאר	CAG	CNC	CNC	THE C	ጥጥር	λλG	TCC	GCC	ልጥር	ccc	GAA	2064
												Ser					2001
20	Pro	Asp		Mec	пуъ	GIII	urs	680	PIIC	PHE	цуз	261	685	Mec	FIO	014	
20			675					000					003				
	ccc	<b>ጥ</b> እ <i>C</i>	GTC.	כאכ	GAG	CGC	ACC	איזיכ	ጥጥር	ידידר	ΔΔG	GAC	GAC	GGC	AAC	TAC	2112
												Asp					
	GIY	690		GIII	Giu	n. 9	695	110	F 11.C	7 110	<i>ک</i> رک	700	1102	<b>-</b> 1		-1-	
25		030					0,5					, , ,					
20	ממ	ACC	CGC	GCC	GAG	GTG	AAG	TTC	GAG	GGC	GAC	ACC	CTG	GTG	AAC	CGC	2160
												Thr					
	705		5			710	-4-			4	715					720	
30	ATC	GAG	CTG	AAG	GGC	ATC	GAC	TTC	AAG	GAG	GAC	GGC	AAC	ATC	CTG	GGG	2208
												Gly					
				•	725		_		-	730	_	_			735		
							•										
	CAC	AAG	CTG	GAG	TAC	AAC	TAC	AAC	AGC	CAC	AAC	GTC	TAT	ATC	ATG	GCC	2256
35	His	Lys	Leu	Glu	Tyr	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	Ala	
				740					745					750			
						-						AAG					2304
	Asp	Lys	Gln	Lys	Asn	Gly	Ile	Lys	Val	Asn	Phe	Lys		Arg	His	Asn	
40			755					760					765				
																7.00	2252
												TAC					2352
			Asp	GIA	Ser	Val		Leu	Ата	Asp	His	Tyr	GIn	Gin	Asn	THE	
45		770					775					780					,
45					~~~		ama	ama.	cma.	~~~	~~		03 C	ma a	OTC.	. אכיכי	2400
												AAC					24,00
		TIE	GIĀ	Asp	GIY		vai	Leu	Leu	PIO		Asn	UIR	ıyı	пеп	800	
	785					790					795					500	
EO	* ~~	(1× C	The co	CCC	CITIC	אממ	מממ	C N C		አአሮ	מאת	AAG	רמר	CAT	CAC	ъπα	2448
50												Lys					
	inr	GIII	ser	WIG	805	ser	nys	wsb	-10	810		- nys	ary	voh	815		
					903					010					010		
	GTC	CTC	<u>ריזירי</u>	GAG	ጥጥር	GTC	אכר	פרר	פרר	GGG	ДΤС	יייאַ י	כייים	GGC	ATG	GAC	2496
55																Asp	
	, ar	u		820					825	_				830		- 4	

131

GAG CTG TAC AAG TAA Glu Leu Tyr Lys 835

5

10

(2) INFORMATION FOR SEQ ID NO:61:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 836 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- 15 (ii) MOLECULE TYPE: protein
  - (v) FRAGMENT TYPE: internal
    - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

								•								
20	Met 1	Glu	Leu	Glu	Asn 5	Ile	Val	Ala	Asn	Thr 10	Val	Leu	Leu	Lys	Ala 15	Arg
	Glu	Gly	Gly	Gly 20	Gly	Lys	Arg	Lys	Gly 25	Lys	Ser	Lys	Lys	Trp 30	Lys	Glu
25	Ile	Leu	Lys 35	Phe	Pro	His	Ile	Ser 40	Gln	Cys	Glu	Asp	Leu 45	Arg	Arg	Thr
	Ile	Asp 50	Arg	Asp	Tyr	Cys	Ser 55	Leu	Cys	Asp	Lys	Gln 60	Pro	Ile	Gly	Arg
	Leu 65	Leu	Phe	Arg	Gln	Phe 70	Сув	Glu	Thr	Arg	Pro 75	Gly	Leu	Glu	Cys	Tyr 80
30	Ile	Gln	Phe	Leu	Asp 85	Ser	Val	Ala	Glu	Tyr 90	Glu	Val	Thr	Pro	Asp 95	Glu
	Lys	Leu	Gly	Glu 100	Lys	Gly	Lys	Glu	Ile 105	Met	Thr	Lys	Tyr	Leu 110	Thr	Pro
35	Lys	Ser	Pro 115	Val	Phe	Ile	Ala	Gln 120	Val	Gly	Gln	Asp	Leu 125	Val	Ser	Gln
	Thr	Glu 130	Glu	Lys	Leu	Leu	Gln 135	Lys	Pro	Cys	Lys	Glu 140	Leu	Phe	Ser	Ala
	Cys 145	Ala	Gln	Ser	Val	His 150	Glu	Tyr	Leu	Arg	Gly 155	Glu	Pro	Phe		Glu 160
40	Tyr	Leu	Asp	Ser	Met 165	Phe.	Phe	Asp	Arg	Phe 170	Leu	Gln	Trp	Lys	Trp 175	Leu
	Glu	Arg	Gln	Pro 180	Val	Thr	Lys	Asn	Thr 185	Phe	Arg	Gln	Tyr	Arg 190	Val	Leu
45	Gly	Lys	Gly 195	Gly	Phe	Gly	Glu	Val 200	Cys	Ala	Cys	Gln	Val 205	Arg	Ala	Thr
	Gly	Lys 210	Met	Tyr	Ala	Сув	Lys 215	Arg	Leu	Glu	Lys	Lys 220	Arg	Ile	Lys	Lys
	Arg 225	Lys	Gly	Glu	Ser	Met 230	Ala	Leu	Asn	Glu	Lys 235	Gln	Ile	Leu	Glu	Lys 240
50	Val	Asn	Ser	Gln	Phe 245	Val	Val	Asn	Leu	Ala 250	Tyr	Ala	Tyr	Glu	Thr 255	Lys
	Asp	Ala	Leu	Cys 260		Val	Leu	Thr	Ile 265		Asn	Gly	Gly	Asp 270	Leu	Lys
	Phe	His	Ile		Asn	Met	Gly	Asn		Gly	Phe	Glu	Glu		Arg	Ala

131

280 Leu Phe Tyr Ala Ala Glu Ile Leu Cys Gly Leu Glu Asp Leu His Arg

							205					200				
		290	<b>671</b>	**- 7	M	<b>3</b>	295	7	T	Dwa	<i>a</i> 1	300	Tla	LON	J. OU	752
		ASII	THE	vaı	Tyr		Asp	neu	пуя	PIO	315	ASII	116	пеп	пец	320
	305	<b></b>	a1	*** -	Ile	310	T1.	C - ~	7 ~~	Ton		Lou		นาไ		
5	Asp	туг	GIY	HIS	325	Arg	116	ser	Asp	330	GIY	Deu	ATG	vai	335	116
	Pro	Glu	Gly		Leu	Ile	Arg	Gly		Val	Gly	Thr	Val		Tyr	Met
		_	<b>~</b> 1	340	•	3	<b>&gt;</b>	<b>01</b>	345	TL	<b>a</b> 1	Y 011	C	350	7.00	T-1
	Ala	Pro	355	vaı	Leu	Asn	ASN	360	Arg	гуг	GIY	Leu	365	PIO	Asp	ıyı
10	Trp	Gly	Leu	Gly	Сув	Leu	Ile	Tyr	Glu	Met	Ile	Glu	Gly	Gln	Ser	Pro
	_	370					375					380				
	Phe	Arg	Gly	Arg	Lys		Lys	Val	Lys	Arg		Glu	Val	Asp	Arg	
	385	_		_,		390	7		<b>a</b>	! <u>-</u>	395	<b>D</b> b -	0	<b>~</b> 1	<b>~</b> 1	400
45	Val	Leu	Glu	Thr	Glu	GIU	vaı	Tyr	Ser		ьуѕ	Pne	ser	GIU	415	Ala
15	<b>*</b> ·	0	Tla	Cura	405 Lys	Mat	Lau	Ton	Thr	410	) an	ב [ מ	Lve	Gln		I.e.
	гуз	Ser	116	420	пув	Mec	Leu	Dea	425	шyъ	veħ	AIG	Буб	430	my	200
	Glv	Cve	Gln		Glu	Glv	Ala	Δla		Val	Lvs	Ara	His		Phe	Phe
	Gry	Cyb	435		<b>01</b>	017		440	-		-1-	5	445			
20	Ara	Asn		Asn	Phe	Lvs	Ara		Glu	Ala	Gly	Met	Leu	Asp	Pro	Pro
		450				_, _	455				•	460		-		
	Phe		Pro	Asp	Pro	Arg	Ala	Val	Tyr	Cys	Lys	Asp	Val	Leu	Asp	Ile
	465			-		470					475					480
	Glu	Gln	Phe	Ser	Thr	Val	Lys	Gly	Val		Leu	Asp	His	Thr		Asp
25					485					490	<b>-</b>	_		_	495	<b>~1</b>
	Asp	Phe	Tyr		Lys	Phe	Ser	Thr		Ser	Val	Ser	IIe		Trp	GIN
	_	<b>~</b> 3.	No - 4-	500	<b>a</b> 1	m\	<b>63</b>	<b>~</b>	505	Y	<b>~1</b>	T 011	7	510	Dhe	Glv
	Asn	Gin		11e	Glu	Thr	GIU	520	Pne	ьys	GIU	Leu	525	vaı	PHE	GLY
30	Dro	A c n	515	Thr	Leu	Pro	Pro		T.e.ii	Δgn	Δτα	Δen		Pro	Pro	Glu
30	PIO	530	Gry	1111	neu	FIO	535	App	Leu	71011	**** 9	540	••••			
	Pro		Lvs	Lvs	Glv	Leu		Gln	Arq	Leu	Phe		Arq	Gln	His	Gln
•	545		-1-		2	550			_		555	-	٦.			560
		Asn	Ser	Lys	Ser	Ser	Pro	Ser	Ser	Lys	Thr	Ser	Phe	Asn	His	His
35			,		565					570					575	
	Ile	Asn	Ser	Asn	His	Val	Ser	Ser	Asn	Ser	Thr	Gly	Ser	Ser	Arg	Asp
				580					585			_		590		
	Pro	Pro	Val	Ala	Thr	Met	Val	Ser	Lys	Gly	Glu	Glu		Phe	Thr	Gly
		_	595		_			600	_		_		605	<b>01</b>	<b>**</b>	<b>T</b>
40	Val		Pro	Ile	Leu	Val			Asp	GIĀ	Asp			GIA	HIS	Lys
	-1	610	**- 1		<b>~</b> 3	<b>~1</b>	615		~1·	7.00	ת ז ת	620		Glaz	Tare	Len
		ser	vaı	Ser	GIY	630	GIY	GIU	GIY	Asp	635	1111	TYL	Gry	Lys	Leu 640
	625	Len	Tare	Dhe	Tle		ጥb r	Thr	Glv	Lvs		Pro	Val	Pro	Trp	Pro
45	1111	neu	шуз	FIIC	645	Cyb	1111	1111	Cry	650					655	
40	Thr	Leu	Val	Thr		Leu	Thr	Tvr	Glv			Cys	Phe	Ser		Tyr
				660				-1-	665			•		670		-
	Pro	Asp	His			Gln	His	qaA			Lys	Ser	Ala	Met	Pro	Glu
		_	675		•			680			=		685			
50	Gly	Tyr	Val	Gln	Glu	Arg	Thr	Ile	Phe	Phe	Lys	Asp	Asp	Gly	Asn	Tyr
	·	690					695					700				
	Lys	Thr	Arg	Ala	Glu	Val	Lys	Phe	Glu	Gly			Leu	Val	Asn	Arg
	705					710			_	<b>-</b>	715				-	720
	Ile	Glu	Leu	Lys			Asp	Phe	Lys			Gly	Asn	ılle		Gly
55		_		<b>03.</b>	725		m	<b>.</b>	0	730		17-7	т	. Tl-	735 Met	
	His	гÀг	⊥eu	GIU	ıyr	ASD	TY	ASI	SEI	ure	ASI.	. val	туг	. 116	. MEC	Ala

				740					745					750						
	Asp	Lys	Gln 755	Lys	Asn	Gly	Ile	Lys 760	Val	Asn	Phe	Lys	<b>Ile</b> 765	Arg	His	Asn		•	,	
5	Ile	Glu 770	Asp	Gly	Ser	Val	Gln 775	Leu	Ala	Asp	His	Tyr 780	Gln	Gln	Asn	Thr				
	Pro 785	Ile	Gly	Asp	Gly	Pro 790	Val	Leu	Leu	Pro	Asp 795	Asn	His	Tyr	Leu	Ser 800				
•		Gln	Ser	Ala	Leu 805		Lys	Asp	Pro	Asn 810		Lys	Arg	Asp	His 815					
10	Val	Leu	Leu			Val	Thr	Ala			Ile	Thr	Leu	Gly		Asp				
	Glu	Leu	Tyr 835	820 Lys					825					830				,		
			625																	
15		•	(2)	INE	FORM	TION	1 FOF	SEC	) ID	NO:	52:						•			
		į)		QUEN										•						
				LENC				_	ilrs											
20				STRA					2											
			(ע)	TOPC	)IIOG:	(; <u>1</u> .	ineai	5												
				OLEC		TYPI	E: cI	ANC												
25		(.	LX) I	EMIC	JRE:															
				IAN				_	eque	nce										
				LOC OTI																
30		()	ki) S	EQUI	ENCE	DES	CŘIP:	rion	: SE	Q ID	NO:	62:		•						
														GAG				48		
	Met 1	Ser	Arg	Ser	Lys 5	Arg	Asp	Asn	Asn	Phe 10	Tyr	Ser	Val	Glu	Ile	Gly				
35																				
														AAA Lys				96		
		501		20				-,-	25	-1-				30						
40														GCC			1	44.		
	Gly	Ser	Gly 35	Ala	Gln	Gly	Ile	Val 40	Cys	Ala	Ala	Tyr	Asp 45	Ala	Ile	Leu				
	GAD	AGA	таа	CTT	GCA	אדר	DAG	DAG	СТА	AGC	CGA	CCA	ጥጥጥ	CAG	ААТ	CAG	,	92		
45														Gln			_			
		50					55					60								
														AAA			2	40		
50	Thr 65	His	Ala	rys	Arg	A1a 70	Tyr	Arg	GIu	Leu	75	Leu	Met	Lys	Cys	va1 80				
							000							-	a. ~	71 T				
														. CCA Pro			4	88		
			4 -		85		1		_ <b></b>	90					95	-				
55	TCC	CTA	GAA	GAA	TTT	CAA	GAT	GTT	TAC	ATA	GTC	ATG	GAG	CTC	ATG	GAT	3	336		
																			133	

										104							
	Ser	Leu	Glu	Glu 100	Phe	Gln	Asp	Val	Tyr 105	Ile	Val	Met	Glu	Leu 110	Met	Asp	
	GCA	ТАА	СТТ	TGC	CAA	GTG	АТТ	CAG	ATG	GAG	СТА	GAT	САТ	GAD	AGA	ATG	384
5					Gln												
	TCC	ሞአ 🖰	Стт	CTC	TAT	CNG	አጥር	CTC	TO THE	CCA	አጥሮ	אאמ	CNC	Cum	CAT	TOT	432
					Tyr												732
10		130	200	Dou.	-7-		135	Deu		G ₁		140	•••	Deu		502	
	GCT	GGA	ATT	ATT	CAT	CGG	GAC	TTA	AAG	CCC	AGT	AAT	ATA	GTA	GTA	AAA	480
	Ala	Gly	Ile	Ile	His	Arg	Asp	Leu	Lys	Pro	Ser	Asn	Ile	Val	Val	Lys	
	145					150					155					160	
15									~-~								
					TTG												528
	Ser	Asp	Cys	IIII	Leu 165	пув	116	neu	Asp	170	GIY	ьец	Ala	Arg	175	WIĠ	
20	GGA	ACG	AGT	TTT	ATG	ATG	ACG	CCT	TAT	GTA	GTG	ACT	CGC	TAC	TAC	AGA	576
•	Gly	Thr	Ser	Phe	Met	Met	Thr	Pro	Tyr	Val	Val	Thr	Arg	Tyr	Tyr	Arg	
				180					185					190			
					ATC												624
25	Ala	Pro	G1u 195	Val	Ile	Leu	Gly	Met 200	Gly	Tyr	Lys	Glu	Asn 205	Val	Asp	Leu	
	TGG	TCT	GTG	GGG	TGC	ATT	ATG	GGA	GAA	ATG	GTT	TGC	CAC	AAA	ATC	CTC	672
	Trp	Ser	Val	Gly	Cys	Ile	Met	Gly	Glu	Met	Val	Cys	His	Lys	Ile	Leu	
30		210					215					220					
	արդուր	CCA	GGA	AGG	GAC	יימיי	אידי מ	ርልሞ	CAG	TGG	דממ	מממ	GTT	אייי ב	GAA	CAG	720
					Asp												, 20
	225		1	5		230					235	-1-				240	
35																	
					TGT												768
	Leu	Gly	Thr	Pro	Cys	Pro	Glu	Phe	Met	Lys	Lys	Leu	Gln	Pro		Val	
					245					250					255		
40	AGG	Σ כידי	ፐልሮ	ርጥጥ	GAA	ממ	DCD.	ССТ	מממ	ጥልጥ	CCT	GGA	יימיד	<b>NGC</b>	ւեւնեւն	GAG	816
70					Glu											_	010
•	5		- 4 -	260			5		265	-1-		3	-1-	270		_	
					GAT			_									864
45	Lys	Leu		Pro	Asp	Val	Leu		Pro	Ala	Asp	Ser		His	Asn	Lys	
			275					280					285				•
	Curr	ממת	GCC	λст	CAG	GCA	NGG.	CAT	ייים אינים אינ	עידייז	TOO	מממ	איייב	CTG	CTA	מידה	912
					Gln											_	714
50	#-u	290					295	p		Leu		300					
	GAT	GCA	TCT	AAA	AGG	ATC	TCT	GTA	GAT	GAA	GCT	CTC	CAA	CAC	CCG	TAC	960
		Ala	Ser	Lys	Arg	Ile	Ser	Val	Asp	Glu	Ala	Leu	Gln	His	Pro	Tyr	
	305					310					315					320	
55	* ta-~	7 7 ~~	ama	maa	יים ענות	~~~	~~~	Tr.ca-	<b>~</b>		(I) T	~~~	~~~	~~-		አ አ C	1000
	ATC	AAT	GTC	166	TAT	GAT	CCT	TCT	GAA	GCA	GAA	GCT	CCA	CCA	CCA	AAG	1008

										100							•	
	Ile	Asn	Val	Trp	Tyr 325	Asp	Pro	Ser	Glu	Ala 330	Glu	Ala	Pro	Pro	Pro 335	Lys		
	АТС	CCT	GAC	AAG	CAG	TTA	GAT	GAA	AGG	GAA	CAC	ACA	ATA	GAA	GAG	TGG	1056	•
5				Lys														
				340					345					350				
				ATA													1104	
	Lys	Glu		Ile	Tyr	Lys	Glu		Met	Asp	Leu	Glu		Arg	Thr	rae		
10			355					360					365					
				ATA													1152	
	Asn	370	val	11e	Arg	GIY	375	Pro	ser	Pro	Leu	380	GIN	vai	GIN	Gln .		
15																		
				CCG													1200	
	385	Asp	PIO	Pro	vai	390	inr	Met	vai	ser	дув 395	GIY	GIU	GIU	ьец	400		
	303					3,0		٠										
20				GTG													1248	
	Thr	Gly	Val	Val			Leu	Val	Glu		Asp	Gly	Asp	Val		Gly		
					405	٠				410					415			
	CAC	AAG	TTC	AGC	GTG	TCC	GGC	GAG	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	1296	
25				Ser														
				420					425					430				
	AAG	CTG	ACC	CTG	AAG	TTC	ATC	TGC	ACC	ACC	GGC	AAG	CTG	CCC	GTG	CCC	1344	
	Lys	Leu		Leu	Lys	Phe	Ile	Cys	Thr	Thr	Gly	Lys		Pro	Val	Pro		
30			435					440					445					
	TGG	CCC	ACC	CTC	GTG	ACC	ACC	CTG	ACC	TAC	GGC	GTG	CAG	TGC	TTC	AGC	1392	
				Leu														
		450					455					460						
35	000	ma (1	ccc	GAC	CNC	איזיכ	אאכ	CNG	CAC	GAC	ጥጥር	ייייי	AAG	<b>שרכ</b>	פככ	בידכ	1440	
				Asp													1440	
	465	-1-	•==	F		470	-,-				475					480		
40	CCC	GAA	GGC	TAC	GTC	CAG	GAG	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	1488	
																Gly		
					485					490					495			
	AAC	TAC	AAG	ACC	CGC	GCC	GAG	GTG	AAG	TTC	GAG	GGC	GAC	ACC	CTG	GTG	1536	
45				Thr														
		_	_	500					505					510				
		G00	3 M.C	ana	ama	220	. 000	አመረ	G3.G	mma	220	CAC	CAC	aac	ממ	אייר	1584	
•																ATC Ile	1304	
50	NO.		515			_, 5	,	520			_, 0		525		3-	- <del>-</del>		
•	CTG	GGG	CAC	AAG	CTG	GAG	TAC	AAC	TAC	AAC	AGC	CAC	AAC	GTC	TAT	ATC	1632	
																Ile		
		530		_			535					540						
55		000	<b>03</b> C	770	C N C	**~	n n ~	-	7 m~		- CTO-C	י אר	י יייים יי	י אאר	አጥ⁄	י רפר	1680	
	ATG	GCC	GAC	AAG	CAG	HHG	AAC	GGC	ATC	AAG		AAC	. 110	HHG	AIC	: CGC	1000	1
																		ı

						-				130							
	Met 545	Ala	Asp	Lys	Gln	Lys 550	Asn	Gly	Ile	Lys	Val 555	Asn	Phe	Lys	Ile	Arg 560	,
5							AGC Ser										1728
10							GGC Gly										1776
4.5							CTG Leu										1824
15							TTC Phe 615										1872
20		GAC Asp				AAG Lys 630	TAA										1893
25			(2)	INI	FORM	ATIOI	1 FOI	R SE(	) ID	NO:	63:						
30		(:	(A) (B) (C)	LENG TYPI STRA	ETH: E: ar ANDEI	630 mino ONES	ACTEI amin acio S: s: inean	no ao 1 ingle	cids								
35		. (1	v) Fi	RAGMI	ENT :	TYPE	E: pr : int	erna	al	Q ID	NO:	63:					
	Met 1	Ser	Arg	Ser	Lys 5	Arg	Asp	Asn	Asn	Phe 10	Tyr	Ser	Val	Glu	Ile 15	Gly	
40	_			20			Leu		25					30			
	_		35					40					45			Leu	
45		50					55					60				Val	
	65			_	_	70	_				75				•	. Lys	
50	Ser	Leu	Glu		85 Phe	Gln	Asp	Val			Val	Met	Glu			Asp	
	Ala	Asn	Leu 115	100 Cys	Gln	Val	Ile	Gln 120	105 Met		Leu	Asp	His			Met	
55	Ser	Tyr 130		Leu	Tyr	Gln	Met 135		Сув	Gly	Ile	Lys 140	His		His	Ser	
	Ala		Ile	Ile	His	Arg		Leu	Lys	Pro	Ser	Asn	Ile	Val	Val	Lys	40

	145					150					155					160
•		Asp	Cys	Thr	Leu 165		Ile	Leu	Asp	Phe 170		Leu	Ala	Arg	Thr 175	
-	Gly	Thr	Ser			Met	Thr	Pro	_		Val	Thr	Arg	Tyr		Arg
5	Ala	Pro		180 Val	Ile	Leu	Gly		185 Gly	Tyr	Lys	Glu		190 Val	Asp	Leu
•	Trp	Ser	195 Val	Gly	Сув	Ile	Met	200 Gly	Glu	Met	Val	Cys	205 His	Lys	Ile	Leu
10	Phe	210 Pro	Gly	Arg	Asp	Tyr	215 Ile	Asp	Gln	Trp	Asn	220 Lys	Val	Ile	Glu	Gln
	225		_,	_	_	230				_	235	_		_		240
٠		_			245					250				Pro	255	
15	_			260			_		265	_			_	Ser 270		
	Lys	Leu	Phe 275	Pro	Asp	Val	Leu	Phe 280	Pro	Ala	Asp	Ser	Glu 285	His	Asn	Lys
	Leu	Lys 290	Ala	Ser	Gln	Ala	Arg 295	-	Leu	Leu	Ser	Lys 300	Met	Leu	Val	Ile
20	Asp 305	Ala	Ser	Lys	Arg	Ile 310	Ser	Val	Asp	Glu	Ala 315	Leu	Gln	His	Pro	Tyr 320
	Ile	Asn	Val	Trp	Tyr 325	Asp	Pro	Ser	Glu	Ala 330	Glu	Ala	Pro	Pro	Pro 335	Lys
25	Ile	Pro	qaA	Lys 340	Gln	Leu	qaA	Glu	Arg 345	Glu	His	Thr	Ile	Glu 350	Glu	Trp
	Lys	Glu	Leu 355	Ile	Tyr	Lys	Glu	Val 360	Met	Asp	Leu	Glu	Glu 365	Arg	Thr	Lys
	Asn	Gly 370	Val	Ile	Arg	Gly	Gln 375	Pro	Ser	Pro	Leu	Ala 380	Gln	Val	Gln	Gln
30	Trp 385	Asp	Pro	Pro	Val	Ala 390	Thr	Met	Val	Ser	Lys 395	Gly	Glu	Glu	Leu	Phe 400
	Thr	Gly	Val	Val	Pro 405	Ile	Leu	Val	Glu	Leu 410	Asp	Gly	Asp	Val	Asn 415	Gly
35	His	Lys	Phe	Ser 420	Val	Ser	Gly	Glu	Gly 425	Glu	Gly	Asp	Ala	Thr 430	Tyr	Gly
	Lys	Leu	Thr 435	Leu	Lys	Phe	Ile	Cys	Thr	Thr	Gly	Lys	Leu 445	Pro	Val	Pro
	Trp	Pro 450	Thr	Leu	Val	Thr	Thr 455	Leu	Thr	Tyr	Gly	Val 460	Gln	Cys	Phe	Ser
40	Arg 465		Pro	Asp	His	Met		Gln	His	qaA	Phe 475		Lys	Ser	Ala	Met 480
		Glu	Gly	Tyr	Val 485		Glu	Arg	Thr	Ile 490		Phe	Lys	Asp	Asp	Gly
45	Asn	Tyr	Lys			Ala	Glu	Val	-		Glu	Gly	Asp	Thr 510		Val
40	Asn	Arg		500 Glu	Leu	Lys	Gly		505 Asp	Phe	Lys	Glu	Asp 525		Asn	Ile
•	Leu	_	515 His	Lys	Leu	Glu	_	520 Asn	Tyr	Asn	Ser			Val	Tyr	Ile
50		530 Ala	Asp	Lys	Gln		535 Asn	Gly	Ile	Lys		540 Asn	Phe	Lys	Ile	Arg
	545 His	Asn	Ile	Glu		550 Gly	Ser	Val	Gln		555 Ala	Asp	His	Tyr		560 Gln
55	Asn	Thr	Pro	Ile 580	565 Gly	Asp	Gly	Pro	Val 585	570 Leu	Leu	Pro	Asp	Asn 590	575 His	Tyr
JJ	Leu	Ser	Thr		Ser	Ala	Leu	Ser	_	Asp	Pro	Asn	Glu		Arg	Asp

									•									
•		610						600 Val	Thr	Ala .			605 Ile '	Thr	Leu	Gly	•	
5	Met . 625	Asp	Glu	Leu	-	Lys 630												
			(2)	INF	ORMA	TION	FOR	SEQ	ID	NO : 6	4:							
10		(i	(A) (B) (C)	QUEN LENG TYPE STRA TOPO	TH: : nu NDEL	1821 clei NESS	bas c ac	e pa id ngle	irs									
15				OLEC		TYPE	: cD	AN			•							
20		(5	(B) (D)	NAM LOC OTH	ATIC	N: I	1 RMATI	818 ON:			NO · 6	: <b>4</b> ·						
		()	(1) 2	PLOOP	MCE	DESC	.KIPI	LON	SEC	, ID	140:6							
25													CTG Leu				48	
30													CCA Pro				96	
0.5													AAA Lys 45				144	
35													TCC Ser				192	
40													CAT				240	
45													GCA Ala			Leu	288	
50																GAT Asp	336	
									Lys					His		CAG Gln	384	
55	TTC	CTT	ATC	TAC	CAA	. ATT	CTC	CGA	GGT	CTA	AAG	TAT	' ATA	CAT	TCA	GCT	432	138

																	Ē	
	Phe	Leu 130	Ile	Tyr	Gln	Ile	Leu 135	Arg	Gly	Leu	Lys	Tyr 140	Ile	His	Ser	Ala		
5														GTG Val			480	
10														CAC His			528.	
4.6														GCT Ala 190			576	
15														ATT Ile			624	
20														TTG Leu			672	
25														CTC Leu			720	
30														TCT Ser			768	
2E	AAC Asn	TAT Tyr	ATT Ile	CAG Gln 260	TCT Ser	TTG Leu	ACT Thr	CAG Gln	ATG Met 265	CCG Pro	AAG Lys	ATG Met	AAC Asn	TTT Phe 270	GCG Ala	AAT Asn	816	
35				Gly					Ala					GAG Glu			864	
40	CTT Leu	GTA Val 290	Leu	GAC Asp	TCA Ser	GAT Asp	AAG Lys 295	Arg	ATT	ACA Thr	GCG Ala	GCC Ala 300	Gln	GCC Ala	CTT Leu	GCA Ala	912	
45		Ala					Tyr					Asp				GCC Ala 320	960	
50						Ser					Asp					GAG Glu	1008	
					Thr					. Ile					Pro	CCC Pro	1056	
55	CTI	GAC	CAA	A GAA	GAC	ATC	GAC	TCC	GA(	GAT	CCF	A CCC	GT(	C GCC	ACC	E ATG	1104	139

	Leu	Asp	Gln 355	Glu	Glu	Met	Glu	Ser 360		Asp	Pro-	Pro	Val 365	Ala	Thr	Met		
5				GGC Gly												_	1152	
10				GGC Gly													1200	
45				GAT Asp											_		1248	
15				AAG Lys 420													1296	
20				GTG Val													1344	
25 [.]				TTC Phe											_		1392	
30				TTC Phe													1440	
				GGC Gly													1488	
35				GAG Glu 500													1536	
40	TAC Tyr			CAC His													1584	
45				AAC Asn									Asp				1632	
50		Leu					Gln					Ile				CCC Pro 560	1680	
											Thr					AGC Ser	1728	
55	AAA	GAC	ccc	AAC	GAG	AAG	CGC	GAT	CAC	ATG	GTC	CTG	CTG	GAG	TTC	GTG	1776	140

				•						• • •		•					
	Lys	Asp	Pro	Asn 580	Glu	Lys	Arg	Asp	His 585	Met	Val	Leu	Leu	Glu 590	Phe	Val	
	ACC	GCC	GCC	GGG	ATC	ACT	CTC	GGC	ATG	GAC	GAG	CTG	TAC	AAG	TAA		1821
5				Gly													
_			595					600		_			605				·
٠												į					
40			(2)	INF	ORMA	MOITA	FOF	SEC	) ID	NO: 6	55:						
10		( j	L) SI	EQUEN	ICE (	CHARA	CTEF	RISTI	cs:								
			(A)	LENG	TH:	606	amir	o ac									
				TYPE					_								
15				STRA				-	=								
.0		•	ι_,														
				MOLEC RAGME													
20		(2	ci) S	SEQUE	ENCE	DESC	RIP	CION	: SE	Q ID	NO : 6	55:					
	Met	Ser	Gln	Glu	Ara	Pro	Thr	Phe.	Tvr	Ara	Gln	Glu	Leu	Asn	Lvs	Thr	
	1	Der		O14	5	110		10	-7-	10	01				15		
25	Ile	Trp	Glu	Val 20	Pro	Glu	Arg	Tyr	Gln 25	Asn	Leu	Ser	Pro	Val	Gly	Ser	
25	Gly	Ala	Tyr	Gly	Ser	Val	Cys	Ala		Phe	Asp	Thr	Lys		Gly	Leu	
	<b>3</b>	17- 1	35	Val	T	T 110	T 033	40 50~	7~~	Dro	Dhe	Gln	45 Ser	Tle	Tle	Hig	
	Arg	va. 50	Ald	Val	пλя	цуѕ	55	Ser	Arg	PIO	FIIC	60	261	110	110	1110	
30		Lys	Arg	Thr	Tyr		Glu	Leu	Arg	Leu		Lys	His	Met	Lys		
	65 Glu	Δen	Val	Ile	Glv	70 Len	Len	Asn	Val	Phe	75 Thr	Pro	Ala	Ara	Ser	80 Leu	
	GIU	Ÿ	• • • • • • • • • • • • • • • • • • • •		85	Deu	200	·p		90				5	95		
	Glu	Glu	Phe	Asn	Asp	Val	Tyr	Leu		Thr	His	Leu	Met		Ala	Asp	
35	Len	Asn	Asn	100 Ile	Val	Lvs	Cvs	Gln	105 Lvs	Leu	Thr	asp	Asp	110 His	Val	Gln	
	204		115			-1-	-1-	120	-1-			•	125				
	Phe			Tyr	Gln	Ile			Gly	Leu	Lys			His	Ser	Ala	
40	Asn	130 Tle		His	Ara	Aspi	135 Leu		Pro	Ser	Asn	140 Leu		Val	Asn	Glu	
40	145	110			5	150		-1-			155					160	•
	Asp	Cys	Glu	Leu			Leu	qaA	Phe			Ala	Arg	His			
	Aen	Glu	Met	Thr	165		Val	Ala	Thr	170 Arg		Tvr	Ara	Ala	175 Pro		
45	veb	Olu	.,,,,	180	UL1	-1-			185			-1-	5	190			
	Ile	Met		Asn	Trp	Met	His			Gln	Thr	Val			Trp	Ser	
	Val	Glv	195 Cvs		Met	Ala	Glu	200 Leu		Thr	Glv	Arq	205 Thr		Phe	Pro	
		210	-				215					220					
50	-	Thr	Asp	His	Ile			Leu	Lys	Leu			Arg	Leu	Val	Gly 240	
	225 Thr	Pro	Glv	בום	Glu	230 Leu		Jive	Jave	Tle	235 Ser		Glu	Ser	Ala	Arg	
	THE	FIO	ary	ard	245		_cu	ە رى	- Ly E	250					255		
55	Asn	Tyr	Ile	Gln 260		Leu	Thr	Gln	Met 265		Lys	Met	Asn	Phe 270		Asn	
JJ	Val	Phe	Ile			Asn	Pro	Leu			Asp	Leu	Lev			Met	

			275					280					285			
	Leu	Val 290	Leu	Asp	Ser	Asp	Lys 295	Arg	Ile	Thr	Ala	Ala 300	Gln	Ala	Leu	Ala
_			Tyr	Phe	Ala			His	Asp	Pro			Glu	Pro		Ala 320
5	305 Asp	Pro	Tyr	Asp	Gln	310 Ser	Phe	Glu	Ser	Arg	315 Asp	Leu	Leu	Ile		
	Trn	Lve	Ser	T.e.:	325 Thr	Tvr	Δsp	Glu	Val	330 Ile	Ser	Phe	Val	Pro	335 Pro	Pro
	-	-		340					345					350		
10		_	355					Ser 360					365			
	Val	Ser 370	Lys	Gly	Glu	Glu	Leu 375	Phe	Thr	Gly	Val	Val 380	Pro	Ile	Leu	Val
45			Asp	Gly	Asp	Val	Asn	Gly	His	Lys	Phe 395	Ser	Val	Ser	Gly	Glu 400
15	385 Gly	Glu	Gly	Asp			Tyr	Gly	ГÀЗ			Leu	Lys	Phe	Ile 415	
	Thr	Thr	Gly	Lys	405 Leu	Pro	Val	Pro	Trp	410 Pro	Thr	Leu	Val			Leu
20	Thr	Tyr	Gly	420 Val	Gln	Cys	Phe	Ser	425 Arg	Tyr	Pro	Asp	His	430 Met	Lys	Gln
	,	-	435		•			440					445			Arg
•		450					455					460				
25	465					470					475					Val 480
	Lys	Phe	Glu	Gly	Asp 485	Thr	Leu	Val	Asn	Arg 490		Glu	Leu	ГÀг	Gly 495	Ile
	Asp	Phe	Lys	Glu 500		Gly	Asn	Ile	Leu 505	Gly	His	Lys	Leu	Glu 510		Asn
30	Tyr	Asn				Val	Tyr		Met	Ala	Asp	Lys	Gln 525	Lys		Gly
	Ile	_		Asn	Phe	Lys				Asn	Ile		Asp		Ser	Val
	Gln	530 Leu		Asp	His	Tyr	535 Gln		Asn	Thr	Pro	540 Ile		Asp	Gly	Pro
35	545			•		550					555					560 Ser
					565					570					575	i
				580					585					590	)	. Val
40	Thr	Ala	Ala 595		Ile	Thr	Leu	Gly 600		Asp	Glu	Leu	605	Lys	ŀ	
			(2	) IN	FORM	ATIO	N FC	R SE	Q ID	NO:	66:					
45		. (	-					RIST								
			(B)	TYP	E: n	ucle	ic a			•						
					ANDE			ingl ir	.e							
50																
			(ii) (ix)				·E: (	:UNA								
								ing S		ence						
55			(E	s) LC	JCAT I	.UN:	1	.2910	,							

(D) OTHER INFORMATION:

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

5				GAG Glu														48
10				GAA Glu 20														96
15				TCC Ser												GCC Ala		144
				GAA Glu														192
20				GAC Asp														240
25				CCT Pro														288
30	GTT Val	GCA Ala	CCA Pro	GGT Gly 100	TCT Ser	TCG Ser	AAA Lys	ACT Thr	GAA Glu 105	GCA Ala	GAT Asp	GTT Val	GAÁ Glu	CAA Gln 110	CAA Gln	GCT Ala		336
35	TTG Leu	ACT Thr	CTC Leu 115	CCG Pro	GAT Asp	CTT Leu	GCA Ala	GAG Glu 120	CAG Gln	TTT Phe	GCC Ala	CCT Pro	CCT Pro 125	GAC Asp	ATT	GCC Ala		384
			Leu	CTT Leu									Lys					432
40		Cys		ACT Thr			Arg					Ser				GAA Glu 160		480
45	TTA Leu	. CGA . Arg	CAG Gln	CTT Leu	CTT Leu 165	GAT Asp	TGT Cys	GAT Asp	ACA Thr	Pro	Ser	GTG Val	Asp	TTG Leu	GAA Glu 175		,	528
50					Val					Phe					Leu	GAC Asp		576
55	Lev	Pro	195	Pro	Val	Ile	Pro	200	a Ala	Val	. Туі	Ser	Glu 205	Met	: Ile	TCT Ser		624
<del>-</del>	TTA	A GCI	CCA	GAA	GTA	CAA	AGC	TCC	GAA	GA#	A TA:	TTA 1	CAG	CTP	Y TTO	AAG		672

	Leu	Ala 210	Pro	Glu	Val	Gln	Ser 215	Ser	Glu	Glu	Tyr	Ile 220	Gln	Leu	Leu	Lys	
5														CTT Leu			720
10														TCC Ser			768
														CCT Pro 270			816
15														CTC Leu			864
20														CAG Gln			912
25														GCC Ala			960
30														TAC Tyr			1008
25			Ser											ACA Thr 350	Ala		1056
35				Leu					Ser					GGT Gly			1104
40								Gly						AAA Lys			1152
45		Arg					Gly					Leu		TTC Phe			1200
50											Glu					TAT	1248
					Asp					Tyr					Tyr	CAA Gln	1296
55	CAG	GAT	CAA	GTT	GTC	AAA	GAA	GAT	LAA 1	TTA '	GAA	GCI	GTA	GGG	AAA	AAA	1344

																	•
,	Gln	Asp	Gln 435	Val	Val	Lys	Glu	Asp 440	Asn	Ile	Glu	Ala	Val 445	Gly	Lys	Lys	
5				TAT Tyr													1392
· .	Arg			GAA Glu		Tyr					Gln					Lys	1440
10				ATT													1488
15				Ile	485					490					495		7526
				ACC Thr 500													1536
20				GGC Gly													1584
25				AAG Lys													1632
30				GAC Asp													1680
				AAC Asn													1728
35				TAC Tyr 580													1776
40				GAG Glu					Glu							TCA Ser	1824
45			Glu	GAT Asp												TGG	1872
50		Val					Arg					Asn				GGG Gly 640	1920
						Phe					Ser					TGC Cys	1968
55	TAT	GCC	TGC	TCT	GTA	GTG	GTG	GAC	: GGC	GAA	. GTA	AAG	CAT	TGT	GTC	ATA	2016 1

	Tyr	Ala	Cys	Ser 660	Val	Val	Val	Asp	Gly 665	Glu	Val	Lys	His	Cys 670	Val	Ile	·	
5														AAC Asn			2064	
10														TCC Ser			2112	
														GTA Val			2160	
15														AGC Ser			2208	•
20														CTG Leu 750			2256	
25														GAG Glu			2304	
30														ACC Thr			2352	
														TAC			2400	
35						Tyr					Lys			GAC Asp			2448	
40										Gln				ATC Ile 830			2496	
45				Gly					Arg					Phe		GGC	2544	
50			Leu					Glu					Asp			GAG Glu	2592	
		Gly					His					Asr				CAC His 880	2640	
55	AAC	GTC	TAT	' ATC	: ATG	GCC	GAC	CAA :	G CAC	DAA E	AAC	: GGC	TA C	: AAG	GTO	AAC	2688	146

SUBSTITUTE SHEET (RULE 26)

									•	147		•					
	Asn	Val	Tyr	Ile	Met 885	Ala	Asp	Lys	Gln	Lys 890	Asn.	Gly	Ile	Lys	Val 895	Asn	
5		AAG Lys															2736
10		TAC Tyr															2784
		AAC Asn 930															2832
.15		AAG Lys															2880
20		ACT Thr									TAA						2913
25			(2)	) IN	FORM	ATIO	N FOI	R.SE	αI Ç	NO:	67:					•	
30		(:	(A) (B) (C)	LEN TYP STR	GTH: E: a: ANDE	970 mino DNES	ACTEI amin acio S: s:	no a d ingl	cids								
35		(-	v) F	RAGM	ENT	TYPE	E: p: : in CRIP	tern	al	Q ID	NO:	67:					
	1	Ser			5					10					15		
40				20				Leu	25				Gly	30		Val Ala	
45		50					55					60				Gly	
	65					70					75					BO BO Pro	
50	-				85 Ser					90 Ala					95 n Glr	n Ala	
			115	Pro	Asp			120	Glr	Phe			125	Ası S	o Ile	e Ala	
55		130	ı				135	;				140	)			y Leu a Glu	

						150					155					160
	145 Leu	N ~~	Gln	T.e.ii	T. <b>a</b> 11		Cvs	Δαη	Thr	Pro		Val	asa	Leu		-
	Leu	Arg	GIII	Бец	165	Agb	Cys	пор		170					175	
	Tle	Asp	Val	His		Leu	Ala	Asp			Lys	Arg	Tyr	Leu	Leu	Asp
5 .	110			180					185		-		-	190		_
U	Leu	Pro	Asn		Val	Ile	Pro	Ala		Val	Tyr	Ser	Glu	Met	Ile	Ser
			195					200			-		205			
	Leu	Ala	Pro	Glu	Val	Gln	Ser	Ser	Glu	Glu	Tyr	Ile	Gln	Leu	Leu	Lys
		210		•		,	215					220				
10	Lys	Leu	Ile	Arg	Ser	Pro	Ser	Ile	Pro	His	Gln	Tyr	Trp	Leu	Thr	Leu
	225					230					235					240
	Gln	Tyr	Leu	Leu	Lys	His	Phe	Phe	Lys	Leu	Ser	Gln	Thr	Ser		Lys
					245					250		_•	_	_	255	•
	Asn	Leu	Leu		Ala	Arg	Val	Leu		Glu	Ile	Phe	Ser	Pro	Met	Leu
15				260		_	_	_	265	•	m\	Gl.,	7	270	T10	Tura
	Phe	Arg		Ser	Ala	Ala	Ser		qaA	Asn	Thr	GIU	285	Leu	TIE	гур
			275	<b>-</b> 1 -	<b>T</b>	<b>~</b> 1_		280	<b>~</b> 1	<b>П~</b> ~	705	Glu		Gln	Dro	λla
	Val		GIU	TTE	гел	тте	295	THE	GIU	пр	ASII	300	мц	Gln	110	7,20
-	D	290	T 011	D~o	D×o	Lve		Dro	Lare	Dro	Thr		Va 1	Ala	Asn	Asn
20	305	Ala	ьеu	PIO	PIO	310	PLO	FIU	шуз	rio	315		• • • • • • • • • • • • • • • • • • • •			320
		Met	Asn	Asn	Asn		Ser	Leu	Gln	Asn		Glu	Trp	Tyr	Trp	Gly
	GIY	1100	71011		325					330			•	•	335	-
	Asp	Ile	Ser	Arq		Glu	Val	Asn	Glu	Lys	Leu	Arg	Asp	Thr	Ala	Asp
25	F			340					345	_				350		
	Gly	Thr	Phe	Leu	Val	Arg	Asp	Ala	Ser	Thr	Lys	Met	His	Gly	Asp	Tyr
	_		355					360					365			
	Thr	Leu	Thr	Leu	Arg	Lys	Gly	Gly	Asn	Asn	Lys	Leu	Ile	Lys	Ile	Phe
		370					375					380			_	_
30	His	Arg	qaA	Gly	Lys	Tyr	Gly	Phe	Ser	Asp		Leu	Thr	Phe	Ser	
	385	_	_			390		_	_	_	395	<b>a</b>	<b>T</b>	N1 -	<b>~1</b> -	400
	Val	Val	Glu	Leu		Asn	His	Tyr	Arg			ser	Leu	Ala	415	TYL
	_		•	•	405	11-1	T	T 011	T 0.11	410		v-1	Car	Larg		Gln
05	Asn	Pro	ьys			vaı	ьys	ьeu	425	IÀT	PIO	Val	261	Lys 430	- 7 -	U
35	<b>01</b> -	7	<i>(</i> 1) =	420		Larg	Gl v	Λen		Tle	Glu	Δla	Val	Gly	Lvs	Lvs
	GIN	Asp	435	vai	vaı	пуь	Giu	440	N311	110	014	****	445	0-1		1
	Len	uia		ጥህጕ	Δen	Thr	Gln		Gln	Glu	Lvs	Ser		Glu	Tyr	Asp
	пец	450		-1-	*****		455				-1-	460			•	-
40.	Ara			Glu	Glu	Tyr	Thr	Arg	Thr	Ser	Gln	Glu	Ile	Gln	Met	Lys
	465					470					475					480
	Arg	Thr	Ala	Ile	Glu	Ala	Phe	Asn	Glu	Thr	Ile	Lys	Ile	Phe	Glu	Glu
					485					490					495	
	Gln	Сув	Gln	Thr	Gln	Glu	Arg	Tyr	Ser	Lys	Glu	Tyr	Ile			Phe
45				500					505					510		_
	Lys	Arg	Glu	Gly	Asn	Glu	Lys	Glu	Ile	Gln	Arg	Ile			Asn	Tyr
			515					520				_	525			
	Asp	Lys	Leu	Lys	Ser	Arg			Glu	Ile	: Ile			Arg	Arg	Arg
		530				_	535					540		. 01	T10	, non
50			Glu	Asp	Leu			GIn	Ala	Ale			Arg	GIU	1 116	Asp 560
	545	_				550			. 7		555			. Arc	, T.326	
	Lys	Arg	met	. AST			: nAs	Pro	Asp	ьеч 570		: GII	י הפנ	. wr	575	Thr
	n	, h~-	ر. مات	T1.7~	565 . T.e.i		. m	. T.e.	ጥኮ፦			e Glv	/ Val	Arc		Lys
55	Arg	Asp	GII	. 191 580			. 1TF	, חבר	585		. wys	1	, , , ,	590		-1-
ນນ	T	יים. ד	Aen			ים. ד	ינט ו	, Ner			ı Thi	c Glı	ı Asr			Ser
	пÀВ	י הבת	. wer			- שכנ	נים י	, upi			- 4111		t		1-	

			595					600					605			
	Leu	Val 610		Asp	Asp	Glu	Asp 615	Leu	Pro	His	His	Asp 620	Glu	Lys	Thr	Trp
	Asn		Gly	Ser	Ser	Asn	Arg	Asn	Lys	Ala	Glu	Asn	Leu	Leu	Arg	Gly
5	625					630					635					640
	Lys	Arg	Asp	Gly	Thr 645	Phe	Leu	Val	Arg	Glu 650	Ser	Ser	Lys	Gln	Gly 655	Cys
	Tyr	Ala	Cys	Ser 660		Val	Val	Asp	Gly 665		Val	Lys	His	Cys 670		Ile
10	Asn	Lys	Thr 675		Thr	Gly	Tyr	Gly 680		Ala	Glu	Pro	Tyr 685	Asn	Leu	Tyr
	Ser			Lys	Glu	Leu			His	Tyr	Gln			Ser	Leu	Val
	Gln	690 His	Asn	Asp	Ser	Leu	695 Asn	Val	Thr	Leu	Ala	700 Tyr	Pro	Val	Tyr	Ala
15	705					710					715					720
			-		725					730				Ser	735	
	Glu	Glu	Leu	Phe 740	Thr	Gly	Val	Val	Pro 745	Ile	Leu	Val	Glu	Leu 750	Asp	Gly
20	Asp	Val	Asn 755	Gly	His	Lys	Phe	Ser 760	Val	Ser	Gly	Glu	Gly 765	Glu	Gly	Asp
	Ala	Thr 770		Gly	Lys	Leu	Thr 775		Lys	Phe	Ile	Cys 780	Thr	Thr	Gly	Lys
	Leu		Val	Pro	Trp	Pro		Leu	Val	Thr	Thr		Thr	Tyr	Gly	Val
25	785					790					795					800
	Gln	CAe	Phe	Ser	Arg 805	Tyr	Pro	Asp	His	Met 810	Lys	Gln	His	Asp	Phe 815	Phe
	Lys	Ser	Ala	Met 820	Pro	Glu	Gly	Tyr	Val 825	Gln	Glu	Arg	Thr	Ile 830	Phe	Phe
30	Lys	Asp	Asp 835	Gly	Asn	Tyr	Lys	Thr 840	Arg	Ala	Glu	Val	Lys 845	Phe	Glu	Gly
	Asp	Thr 850	Leu	Val	Asn	Arg	Ile 855	Glu	Leu	Lys	Gly	Ile 860	Asp	Phe	Lys	Glu
35	Asp 865		Asn	Ile	Leu	Gly 870		Lys	Leu	Glu	Tyr 875	Asn	Tyr	Asn	Ser	His 880
33		Val	Tyr	Ile	Met 885		Asp	Lys	Gln	Lys 890		Gly	Ile	Lys	Val 895	
	Phe	Lys	Ile	Arg	His	Asn	Ile	Glu	_				Gln	Leu 910	Ala	Asp
40	His	Tyr	Gln 915			Thr	Pro	Ile 920					Val 925	Leu		Pro
	Asp			Tyr	Leu	Ser			Ser	Ala	Leu		Lys	Asp	Pro	Asn
	Glu	930	Ara	Δsn	His	Met	935 Val	Len	Len	Glu	Phe	940 Val		Ala	Ala	Glv
45	945		AT 9	nop		950		10 u	n-u	014	955		~			960
		Thr	Leu	Gly	Met 965	Asp		Leu	Tyr	Lys 970						
					205					210						
			(2	) IN	FORM	OITA	n fo	R SE	Q ID	NO:	68:					
50	•															

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1788 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- 55 (D) TOPOLOGY: linear

150

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION: 1...1785

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

		(x	:i) S	EQUE	NCE	DESC	RIPT	'ION:	SEC	ID	NO : 6	8:						
10														GAG Glu				48
15														AAA Lys 30				96
20	GAC Asp	CCC Pro	TCT Ser 35	CAG Gln	TAA Asn	ACA Thr	GCC	CAG Gln 40	TTG. Leu	GAT Asp	CAG Gln	TTT	GAT Asp 45	AGA Arg	ATC Ile	AAG Lys	1	44
25														AAG Lys			1	92
25														CAG Gln			2	40
30	GTG Val	AAG Lys	CTA Leu	AAG Lys	CAG Gln 85	ATC Ile	GAG Glu	CAC His	ACT Thr	CTG Leu 90	AAT Asn	GAG Glu	AAG Lys	CGC Arg	ATC Ile 95	CTG Leu	2	88
35	CAG Gln	GCC Ala	GTC Val	AAC Asn 100	TTC Phe	CCG Pro	TTC Phe	CTG Leu	GTC Val 105	AAA Lys	CTT Leu	GAA Glu	TTC Phe	TCC Ser 110	TTC Phe	AAG Lys	3	36
40	GAC Asp	AAC Asn	TCA Ser 115	Asn	CTG Leu	TAC Tyr	ATG Met	GTC Val 120	Met	GAG Glu	TAT	GTA Val	GCT Ala 125	GGT Gly	GGC	GAG Glu	3	. 84
45	Met	Phe 130	Ser	His	Leu	Arg	Arg 135	Ile	Gly	Arg	Phe	Ser 140	Glu	CCC Pro	His	Ala	4	132
		Phe					Ile					Glu		CTG			•	480
50	CTG Leu	GAC Asp	Leu	ATC	TAC Tyr 165	Arg	GAC Asp	CTG Lev	AAG Lys	CCC Pro	Glu	TAA E	CTI Lev	CTC Leu	ATC Ile	qaA		528
55	CAG Glr	CAG Gln	GGC Gly	TAT Tyr 180	Ile	CAG Gln	GTG Val	ACA Thr	A GAC Asp 185	Phe	GG7 Gly	r TTI / Phe	GCC Ala	AAG Lys 190	Arg	GTG Val		576

F	AAA Lys	GGC	CGT Arg 195	ACT Thr	TGG Trp	ACC Thr	TTG Leu	TGT Cys 200	GGG Gly	ACC Thr	CCT Pro	GAG Glu	TAC Tyr 205	TTG Leu	GCC Ala	CCC Pro	624
5		ATT Ile 210															672
10		GGA Gly															720
15	Ala	GAC Asp	Gln	Pro	Ile 245	Gln	Ile	Tyr	.Glu	Lys 250	Ile	Val	Ser	Gly	Lys 255	Val	768
20	Arg	TTC Phe	Pro	Ser 260	His	Phe	Ser	Ser	Asp 265	Leu	Lys	Asp	Leu	Leu 270	Arg	Asn	816
25	Leu	CTG Leu	Gln 275	Val	Asp	Leu	Thr	Lys 280	Arg	Phe	Gly	Asn	Leu 285	Lys	Asp	Gly	864
	Val	AAT Asn 290	Asp	Ile	Lys	Asn	His 295	Lys	Trp	Phe	Ala	Thr 300	Thr	Asp	Trp	Ile	912
30	Ala 305		Tyr	Gln	Arg	Lys 310	Val	Glu	Ala	Prò	Phe 315	Ile	Pro	Lys	Phe	Lys 320	960
35	Gly		Gly	Asp	Thr 325	Ser	Asn	Phe	Asp	Asp	Tyr	Glu	Glu	Glu	Glu 335	Ile	
40	Arg	GTC Val	Ser	11e 340	Asn	Glu	Lys	Cys	Gly 345	Lys	Glu	Phe	Thr	Glu 350	Phe	Gly	1056
45	Arg	Ala	Met 355	Ser	Lys	Gly	Glu	Glu 360	Leu	Phe	Thr	Gly	Val 365	Val	Pro		1104
	CTI Leu	GTT Val 370	Glu	TTA Leu	GAT Asp	GGC	GAT Asp 375	Val	TAA '	GGG Gly	CAA Gln	AAA Lys 380	Phe	: TCT : Ser	GTT Val	Ser	1152
50							Ala					Leu				TTT Phe 400	1200
55						Lys					Tr					ACT Thr	1248

		CTC Leu															1296
				420				•	425			,		430			
5										. =0		<i>-</i>	~~m	m a m	Cm N	an a	1344
		CAG Gln															1344
	пÀв	GTII	435	Asp	PHE	PHE	пур	440	ATA	Mec	PIO		445	LYL	Val	0111	,
			133					110									
10	GAA	AGA	ACT	ATA	TTT	TAC	AAA	GAT	GAC	GGG	AAC	TAC	AAG	ACA	CGT	GCT	1392
	Glu	Arg	Thr	Ile	Phe	Tyr	Lys	Asp	Asp	Gly	Asn	Tyr	Lys	Thr	Arg	Ala	
		450					455					460					
	GD 2	GTC	7 7 C	mmer	C N N	COTT	CAT	אככ	Cmm	C TTTT	יויממ	אפא	አጥሮ	GNG	מיזיי	<b>λλλ</b>	1440
15		Val															1110
13	465	V 44 1	_,,,			470					475	5				480	
		ATT															1488
	Gly	Ile	Asp	Phe	-	Glu	Asp	Gly	Asn		Leu	Gly	His	Lys		Glu	
20					485					490					495		
	ТΔС	AAT	ТАТ	AAC	TCA	CAT	AAT	GTA	TAC	ATC	ATG	GCA	GAC	AAA	CCA	AAG	1536
		Asn															• •
	•		_	500					505					510			
25																	
		GGC															1584
	Asn	Gly		гÀа	vai	Asn	Pne	ьув 520	ile	Arg	HIS	Asn	525	гув	Asp	GIA	
			515					520					,,,,				
30	AGC	GTT	CAA	TTA	GCA	GAC	CAT	TAT	CAA	CAA	AAT	ACT	CCA	ATT	GGC	GAT	1632
	Ser	Val	Gln	Leu	Ala	qaA	His	Tyr	Gln	Gln	Asn	Thr	Pro	Ile	Gly	Asp	
		530					535					540					
	000	CCT	ama	CMM	TOTO N	CCA	CNC	770	CAT	<b>ም</b> ክ ር	ama	TOO	N.C.C.	י ריא א	ጥርጥ	GCC	1680
35		Pro															1000
00	545					550				-1-	555					560	
					•												
		TCC															1728
	Leu	Ser	Lys	Asp		Asn	Glu	Lys	Arg		His	Met	Ile	Leu		Glu	
40					565		•			570					575		
	ىلىشلىك	СТД	ACA	GCT	GCT	GGG	АТТ	ACA	САТ	GGC	ATG	GAT	GAA	CTA	TAC	AAA	1776
		Val															
				580		•			585			-		590			
45						•											
		CAG															1.788
•	Pro	Gln															
			595														
50																	
			(2	) IN	FORM	ATIO	n Fo	R SE	Q ID	NO:	69:						
		(			NCE										-		
			(A)	LEN	GTH:	595	ami	no a	cids								

- (B) TYPE: amino acid

55

(C) STRANDEDNESS: single

## (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

5

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

÷		(2	11)	) LQUI	SINCE	יייים	JULE	LION.	. DLC	, 10						
٠.,	Met 1	Gly	Asn	Ala	Ala 5	Ala	Ala	Lys	Lys	Gly 10	Ser	Glu	Gln	Glu	Ser 15	Val
10	rys	Glu	Phe	Leu 20	Ala	Lys	Ala	Lys	Glu 25	qaA	Phe	Leu	Lys	10 30	Trp	Glu
	_		35			•		40					45	Arg		
15		50			-		55					60		Lys		
	65					70					75			Gln		80
		-		_	85					90				Arg	95	
20	·			100	•				105					Ser 110		
	_		115					120					125	Gly		
25		130				:	135					140		Pro Leu		
	145		_			150					155			Leu		160
30		_			165		*			170				Lys	175	
30				180					185					190 Leu		
	<del></del>	_	195					200					205	Trp		
35		210					215					220		Pro		,
	225	_				230		•			235			Gly		240
40					245					250				Leu	255	
	Leu	Leu	Gln	260 Val	Asp	Leu	Thr	Lys	265 Arg	Phe	Gly	Asn	Leu	270 Lys	Asp	Gly
	Val	Asn	275 Asp	Ile	Lys	Asn	His	280 Lys	Trp	Phe	Ala	Thr	285 Thr	Asp	Trp	Ile
45	Ala	290 Ile	Tyr	Gln	Arg		295 Val		Ala			300 Ile		Lys	Phe	Lys
	305 Gly		Gly	Asp	Thr	310 Ser		Phe	Asp	Asp	315 Tyr		Glu	Glu		320 Ile
50	Arg	Val	Ser	.Ile	325 Asn	Glu	Lys	Cys				Phe	Thr			Gly
	Arg	Ala		340 Ser	Lys	Gly	Glu				Thr	Gly				Ile
	Leu		355 Glu	Leu	Asp	Gly				Gly	Gln				Val	Ser
55	Gly	370 Glu	Gly	Glu	Gly	Asp	375 Ala		туr	Gly	Lys	380 Leu		Leu	Lys	Phe

-	385					390					395					400		
	Ile	Cys	Thr	Thr	Gly 405	Lys	Leu	Pro	Val	Pro 410	Trp	Pro	Thr	Leu	Val 415	Thr		
5	Thr	Leu	Thr	Tyr 420	Gly	Val	Gln	Cys	Phe 425	Ser	Arg	Tyr	Pro	Asp 430	His	Met		
	Lys	Gln	His 435	Asp	Phe	Phe	Lys	Ser 440	Ala	Met	Pro	Glu	Gly 445	Tyr	Val	Gln		
	Glu	Arg 450	Thr	Ile	Phe	Tyr	Lys 455	qaA	Asp	Gly	Asn	Tyr 460	Lys	Thr	Arg	Ala		
10	465	Val	_			470	_				475					480		
	_	Ile			485					490					495		÷	
15	•	Asn	-	500					505		•			510				
		Gly	515					520					525		,			•
		Val 530					535	·. ·				540						
20	545	Pro				550					555					560		
		Ser	-	_	565			_	_	570					575		,	
25		Val		580	Ala	GIÀ	Ile	Thr	H18	GIÀ	Met	Asp	Glu	ьеи 590	Tyr	тув		
	Pro	Gln	595										,					
30			(2)	INI	FORM	ATIO	N FOI	R SE	Q ID	NO:	70:					·		
00		( :					ACTE							٠				
			(B)	TYPI	E: ni	icle:	ic ad 3: s:	cid										
35							inea	_	-									
				OLEC		TYPI	E: cl	ANC										
40			(B)	LO	CATIO	ON: 3	Codi 1: RMAT	2178	equei	nce	·							
45		(:	ki) s	SEQU	ENCE	DES	CRIP'	rion	: SE	Q ID	NO:	70:						
45																GGG		48
•	Met 1	Ser	Asp	vaı	5 5	TTE	vai	гув	GIU.	10	Trp	Leu	HIS	ьуѕ	15	Gly		
50																GAT Asp		96
55																CGT	1	44

5					AAC Asn												192
5					CGG Arg												240
10					GAA Glu 85												288
15	Glu	Glu	Trp	Thr 100	ACC Thr	Ala	Ile	Gln	Thr 105	Val	Ala	Asp	Gly	Leu 110	Lys	Lys	336
20	Gln	Glu	Glu 115	Glu	GAG Glu	Met	Asp	Phe 120	Arg	Ser	Gly	Ser	Pro 125	Ser	Asp	Asn	384
25	Ser	Gly 130	Ala	Glu	GAG Glu	Met	Glu 135	Val	Ser	Leu	Ala	Lys 140	Pro	ГÀв	His	Arg	432
	Val 145	Thr	Met	Asn	GAG Glu	Phe 150	Glu	Tyr	Leu	Lys	Leu 155	Leu	Gly	Lys	Gly	Thr 160	480
30	Phe	Gly	Lys	Val	ATC Ile 165	Leu	Val	Lys	Glu	Lys 170	Ala	Thr	Gly	Arg	Tyr 175	Tyr	528
35	Ala	Met	Lys	Ile 180		Lys	Lys	Glu	Val 185	Ile	Val	Ala	Lys	Asp 190	Glu	Val	576
40	Ala	His	Thr 195	Leu	ACC Thr	Glu	Asn	Arg 200	Val	Leu	Gln	Asn	Ser 205	Arg	His	Pro	624
45	Phe	Leu 210	Thr	Ala	Leu	Lys	Tyr 215	Ser	Phe	Gln	Thr	His 220	Asp	Arg	Leu		672
	Phe 225	Val	Met	Glu	Tyr	Ala 230	Asn	Gly	gly	Glu	235	Phe	Phe	His	Leu	Ser 240	720
50						Ser					Arg					GAG Glu	768
55	ATT Ile	GTG Val	TCA Ser	GCC Ala 260	Leu	GAC Asp	TAC Tyr	CTC Lev	G CAC 1 His 265	s Sei	GAC Glu	AAC Lys	AAC B ABI	GTC 1 Val 270	l Val	TAC Tyr	816

r		GAC Asp															864
5		ATC Ile 290											Lys				912
10		ATG Met															960
15	CTG Leu	GAG Glu	GAC Asp	AAT Asn	GAC Asp 325	TAC Tyr	GGC Gly	CGT Arg	GCA Ala	GTG Val 330	GAC Asp	TGG Trp	TGG Trp	GGG Gly	CTG Leu 335	GGC Gly	1008
20		GTC Val															1056
25		CAT															1104
	CCG Pro	CGC Arg 370	Thr	CTT Leu	GGT Gly	CCC Pro	GAG Glu 375	GCC Ala	AAG Lys	TCC Ser	TTG Leu	CTT Leu 380	TCA	GGG Gly	CTG Leu	CTC Leu	1152
30	AAG Lys 385	AAG Lys	GAC Asp	CCC Pro	AAG Lys	CAG Gln 390	AGG Arg	CTT	GGC Gly	GGG Gly	GGC Gly 395	TCC Ser	GAG Glu	GAC Asp	GCC Ala	AAG Lys 400	1200
35		ATC Ile									Ile						1248
40	TAC Tyr	GAG Glu	AAG Lys	AAG Lys 420	Leu	AGC Ser	CCA Pro	CCC	TTC Phe 425	Lys	CCC Pro	CAG Gln	GTC Val	ACG Thr 430	Ser	GAG Glu	1296
45	ACT Thr	GAC Asp	ACC Thr 435	Arg	TAT	TTT Phe	GAT Asp	GAG Glu 440	Glu	TTC Phe	ACG Thr	GCC Ala	CAG Gln 445	Met	ATC Ile	ACC Thr	1344
45	ATC Ile	ACA Thr	Pro	CCT Pro	GAC Asp	CAA Gln	GAT Asp 455	Asp	AGC Ser	Met	GAC Glu	TGI Cys 460	Val	GAC Asp	AGC Sei	GAG Glu	1392
50		y Arg					Gln					Ala				GCC Ala 480	1440
55						. Ala					r Lys					TTC Phe	1488

E		GGG Gly															1536
5		AAG Lys															1584
10		CTG Leu 530															1632
15	Trp 545	CCC Pro	Thr	Leu	Val _.	Thr 550	Thr	Leu	Thr	Tyr	Gly 555	Val	Gln	Cys	Phe	Ser 560	1680
20	Arg	TAC Tyr	Pro	Asp	His 565	Met	Lys	Gln	His	Asp 570	Phe	Phe	Lys	Ser	Ala 575	Met	1728
25		GAA Glu															1776
20		TAC Tyr															1824
30		CGC Arg 610															1872
35		GGG Gly															1920
40		GCC Ala															1968
45															Gln	CAG Gln	2016
43				Ile					Val					Asn		TAC Tyr	2064
50			Thr					Ser					Glu			GAT Asp	2112
55		Met					Phe					Gly				GGC Gly 720	2160

158

ATG GAC GAG CTG TAC AAG TAA
Met Asp Glu Leu Tyr Lys
725

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 726 amino acids

- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- 15 (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

20 Met Ser Asp Val Ala Ile Val Lys Glu Gly Trp Leu His Lys Arg Gly Glu Tyr Ile Lys Thr Trp Arg Pro Arg Tyr Phe Leu Leu Lys Asn Asp Gly Thr Phe Ile Gly Tyr Lys Glu Arg Pro Gln Asp Val Asp Gln Arg 25 Glu Ala Pro Leu Asn Asn Phe Ser Val Ala Gln Cys Gln Leu Met Lys 55 Thr Glu Arg Pro Arg Pro Asn Thr Phe Ile Ile Arg Cys Leu Gln Trp 70 75 30 Thr Thr Val Ile Glu Arg Thr Phe His Val Glu Thr Pro Glu Glu Arg 90 Glu Glu Trp Thr Thr Ala Ile Gln Thr Val Ala Asp Gly Leu Lys Lys 105 Gln Glu Glu Glu Met Asp Phe Arg Ser Gly Ser Pro Ser Asp Asn 35 120 Ser Gly Ala Glu Glu Met Glu Val Ser Leu Ala Lys Pro Lys His Arg · 135 Val Thr Met Asn Glu Phe Glu Tyr Leu Lys Leu Leu Gly Lys Gly Thr 150 155 40 Phe Gly Lys Val Ile Leu Val Lys Glu Lys Ala Thr Gly Arg Tyr Tyr 165 170 Ala Met Lys Ile Leu Lys Lys Glu Val Ile Val Ala Lys Asp Glu Val 185 Ala His Thr Leu Thr Glu Asn Arg Val Leu Gln Asn Ser Arg His Pro 45 200 Phe Leu Thr Ala Leu Lys Tyr Ser Phe Gln Thr His Asp Arg Leu Cys 215 Phe Val Met Glu Tyr Ala Asn Gly Gly Glu Leu Phe Phe His Leu Ser 230 235 50 Arg Glu Arg Val Phe Ser Glu Asp Arg Ala Arg Phe Tyr Gly Ala Glu 245 250 Ile Val Ser Ala Leu Asp Tyr Leu His Ser Glu Lys Asn Val Val Tyr 265 Arg Asp Leu Lys Leu Glu Asn Leu Met Leu Asp Lys Asp Gly His Ile 55 280 Lys Ile Thr Asp Phe Gly Leu Cys Lys Glu Gly Ile Lys Asp Gly Ala

		290					295					300				
	Thr 305		Lys	Thr	Phe	Cys 310		Thr	Pro	Glu	Tyr 315		Ala	Pro	Glu	Val 320
5	Leu	Glu	Asp	Asn	Asp 325	Tyr	Gly	Arg	Ala	Val 330	qaA	Trp	Trp	_	Leu 335	Gly
•	Val	Val	Met	Tyr 340	Glu	Met	Met	Cys	Gly 345	Arg	Leu	Pro	Phe	Tyr 350	Asn	Gln
•	Asp	His	Glu 355	Lys	Leu	Phe	Glu	Leu 360	Ile	Leu	Met	Glu	Glu 365	Ile	Arg	Phe
10	Pro	Arg 370	Thr	Leu	.Gly	Pro	Glu 375	Ala	Lys	Ser	Leu	Leu 380	Ser	Gly	Leu	Leu
	385		_		Lys	390	_		-	_	395			-		400
15					His 405					410			-		415	
	•		_	420	Leu				425	-				430		
		_	435	_	Tyr		_	440					445			
20		450			Asp		455	-				460		_		
	465	_			Phe Val	470				_	475					480
25		_			485 Pro					490	_	_			495	
		-		500	Val				505		-	-	_	510		
30		_	515		Lys		_	520	, –		_	_	525			
	Trp	530					535	_				540				
	545 Arg	Tyr	Pro	Asp	His	550 Met	Lys	Gln	His	Asp	555 Phe	Phe	Lys	Ser	Ala	560 Met
35	Pro	Glu	Gly	Tyr	565 Val	Gln	Glu	Arg	Thr	570 Ile	Phe	Phe	Lys	Asp	575 Asp	Gly
	Asn	Tyr	Lys	580 Thr	Arg	Ala	Glu	Val	585 Lys	Phe	Glu	Gly	Asp	590 Thr	Leu	Val
40	Asn	_	595 Ile	Glu	Leu	Lys	-	600 Ile	Asp	Phe	Lys		605 Asp	Gly	Asn	Ile
		610 Gly	His	Lys	Leu		615 Tyr	Asn	Tyr	Asn		620 His	Asn	Val	Tyr	Ile
45	625 Met	Ala	Asp	Lys		630 Lys	Asn	Gly	Ile	_		Asn	Phe	Lys	Ile 655	640 Arg
40	His	Asn	Ile	Glu 660	645 Asp	Gly	Ser	Val	Gln 665	650 Leu		Asp	His	Tyr 670		Gln
	Asn	Thr	Pro 675		Gly	Asp	Gly	Pro 680		Leu	Leu	Pro	Asp 685	Asn	His	Tyr
50	Leu	Ser 690	Thr	Gln	Ser	Ala	Leu 695		Lys	Asp	Pro	Asn 700			Arg	Asp
	His 705			Leu	Leu	Glu 710	Phe	Val	Thr	Ala	Ala 715	Gly	Ile	Thr	Leu	Gly 720
55	Met	Asp	Glu	Leu	Tyr 725	Lys										

		(2)	INI	ORMA	MOITA	I FOF	SEC	) ID	NO:7	2:				
5	(:	(A) (B) (C)	EQUEN LENC TYPI STRA TOPO	ETH: E: nu ANDEI	2751 iclei NESS	bas c ac	se pa cid ingle	airs					·	
10	• -		OLEC		TYPE	E: cI	ANC						. *	
15	(2	(B)	NAM LOC OTI	CATIO	ON: 1 INFOR	RMATI	2748 ION:			NO: 7	72:		٠.	
20			GTT Val											48
			TTC Phe 20											96
25			GAC Asp											144
30			CAC His											192
35			CAA Gln											240
40	 	-	TTC Phe					_						288

ATC AAT GAC CCT AGC CTC TGC GGA ATG GAT CAC ACA GAG AAG AGG GGG 480

GAC CCC AGG AGC AAG CAC AAG TTC AAA ATC CAC ACA TAC GGA AGC CCT Asp Pro Arg Ser Lys His Lys Phe Lys Ile His Thr Tyr Gly Ser Pro

ACC TTC TGT GAT CAC TGT GGG TCC CTG CTC TAT GGA CTT ATC CAC CAA

Thr Phe Cys Asp His Cys Gly Ser Leu Leu Tyr Gly Leu Ile His Gln

GGG ATG AAA TGT GAC ACC TGC GAC ATG AAT GTT CAC AAC CAG TGT GTG

Gly Met Lys Cys Asp Thr Cys Asp Met Asn Val His Asn Gln Cys Val

Ile Asn Asp Pro Ser Leu Cys Gly Met Asp His Thr Glu Lys Arg Gly

												AAG Lys					528
5												·					
	GTA	CGA	GAT	GCA	AAA	TAA	CTA	ATC	CCT	ATG	GAT	CCA	TAA	GGG	CTT	TCG	 576
	Val	Arg	Asp	Ala 180	Lys	Asn	Leu	Ile	Pro 185	Met	Asp	Pro	Asn	Gly 190	Leu	Ser	
10	GAT	CCT	TAT	GTG	AAG	CTG	AAA	CTA	ATC	CCT	GAC	CCC	AAG	TAA	GAG	AGC	624
	-		195		. •			200				Pro	205				
												TAA		_			672
15	Lys	210	гÀз	Thr	ГÀЗ	Thr	215	Arg	Ser	Asn	Leu	Asn 220	Pro	Gin	Trp	Asn	
												AAA					720
20		Ser	Phe	Thr	Phe		Leu	Lys	Pro	Ser	_	Lys	Asp	Arg	Arg	Leu 240	
20	225					230					235					240	
	TCT	GTA	GAA	ATC	TGG	GAC	TGG	GAT	CGG	ACG	ACT	CGG	AAT	GAC	TTC	ATG	768
	Ser	Val	Glu	Ile	Trp	Asp	Trp.	qaA	Arg	Thr	Thr	Arg	Asn	Asp	Phe	Met	
					245					250					255		
25	CCA	יייירירי	Стт	TCC	արար	CCT	מייר	ጥሮል	GNG	CTA	አጥር	AAG	ልጥር	CCG	GCC	ΔСТ	816
												Lys					010
	2			260					265					270			
20	~~-		~~~ <b>~</b>			~~~		~~~	~~~	~~~	~~~	<i>-</i>	m. m	m» a	220	CTC.	864
30												GAA Glu				_	004
			275	_,_				280	014		0-7		285	-1-			
												GAA					912
35	Pro		Pro	Glu	Gly	Asp		Glu	Gly	Asn	Met	Glu	Leu	Arg	GIn	rÀs	
	٠	290					295					300					
	TTT	GAG	AAA	GCC	AAG	CTA	GGT	CCT	GTT	GGT	AAC	AAA	GTC	ATC	AGC	CCT	960
	Phe	Glu	Lys	Ala	Lys		Gly	Pro	Val	Gly		Lys	Val	Ile	Ser		
40	305					310					315					320	
	TCA	GAA	GAC	AGA	AAG	CAA	CCA	TCC	AAC	AAC	CTG	GAC	AGA	GTG	AAA	CTC	1008
												Asp					
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45		a. a	mma		mmc	ama	3 ma		0770	000		000	n cm	mmm.		2 2 C	1056
												GGG Gly					1030
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50												CTG					1104
	Val	Met		Ala	Asp	Arg	Lys	_	Thr	Glu	Glu	Leu		Ala	Ile	Lys	
			355					360					365				
	ATC	CTG	AAG	AAG	GAC	GTG	GTG	ATC	CAG	GAC	GAC	GAC	GTG	GAG	TGC	ACC	1152
55												Asp					
		370					375		•			380					

5																	
5	Mat			AAG											_		1200
5	385	Val	Glu	Lys	Arg	Val 390	Leu	Ala	Leu	Leu	Asp 395	Lys	Pro	Pro	Phe	Leu 400	•
	365					370					درد					100	
		CAG														_	1248
	Thr	Gln	Leu	His		Cys	Phe	Gln	Thr		Asp	Arg	Leu	Tyr	Phe 415	Val	
					405					410					413		
10		GAA				-											1296
	Met	Glu	Tyr		Asn	Gly	Gly	Asp		Met	Tyr	His	Ile	Gln 430	Gln	Val	
÷				420					425					430			
		AAA															1344
15	Gly	Lys		Lys	Glu	Pro	Gln	Ala 440	Val	Phe	Tyr	Ala	Ala 445	Glu	Ile	Ser	
			435					440					773				
		GGA															1392
20	Ile	Gly	Leu	Phe	Phe	Leu	His	Lys	Arg	Gly	Ile	Ile	Tyr	Arg	Asp	Leu	
20		450					433					400					
		CTG															1440
•	Lys 465	Leu	Asn	Asn	Val	Met 470	Leu	Asn	Ser	Glu	Gly 475	His	Ile	Lys.	Ile	A1a 480	
25	405					470					4,5						
		TTC													_		1488
	Asp	Phe	Gly	Met	Cys 485	Lys	Glu	His	Met	Met 490	Asp	GΙΆ	Val	Thr	1nr 495	Arg	
		•															
30		TTC															1536
	Thr	Phe	Cys	500	Thr	Pro	Asp	туг	505	Ala	PIO	GIU	116	510	Ald	TYL	
0.5		CCG															1584
35	Gin	Pro	515	GIY	гуѕ	ser	vai		Trp	Trp	AIA	IÀI		vai	ьeu	Den	
								520					525				
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		GAG						CCT					GAA		_		1632
40		GAG Glu 530						CCT					GAA		_		1632
40	Tyr	Glu 530	Met	Leu	Ala	Gly	Gln 535	CCT Pro	Pro	Phe	Asp	Gly 540	GAA Glu	Asp	Glu	Asp	
40	Tyr GAA	Glu 530 CTG	Met TTT	Leu	Ala	Gly	Gln 535 ATG	CCT Pro	Pro	Phe	Asp	Gly 540 TCC	GAA Glu TAC	Asp	Glu	Asp	1632 1680
40	Tyr GAA	Glu 530 CTG Leu	Met TTT	Leu	Ala	Gly	Gln 535 ATG	CCT Pro	Pro	Phe	Asp	Gly 540 TCC	GAA Glu TAC	Asp	Glu	Asp	
40	Tyr GAA Glu 545	Glu 530 CTG Leu	Met TTT Phe	Leu CAG Gln	TCT Ser	ATA Ile 550	Gln 535 ATG Met	CCT Pro GAG Glu	Pro CAC His	Phe AAC Asn	GTG Val 555	Gly 540 TCC Ser	GAA Glu TAC Tyr	Asp CCC Pro	Glu AAA Lys	TCC Ser	1680
	Tyr GAA Glu 545 TTG	Glu 530 CTG Leu TCC	Met TTT Phe	CAG Gln GAA	Ala TCT Ser	Gly ATA Ile 550 GTC	Gln 535 ATG Met	CCT Pro GAG Glu	CAC His	Phe AAC Asn	GTG Val 555 GGA	Gly 540 TCC Ser	GAA Glu TAC Tyr	CCC Pro	AAA Lys AAA	TCC Ser 560	
	Tyr GAA Glu 545 TTG	Glu 530 CTG Leu	Met TTT Phe	CAG Gln GAA	Ala TCT Ser	Gly ATA Ile 550 GTC	Gln 535 ATG Met	CCT Pro GAG Glu	CAC His	Phe AAC Asn	GTG Val 555 GGA	Gly 540 TCC Ser	GAA Glu TAC Tyr	CCC Pro	AAA Lys AAA	TCC Ser 560	1680
45	Tyr GAA Glu 545 TTG Leu	Glu 530 CTG Leu TCC Ser	TTT Phe AAG Lys	CAG Gln GAA Glu	TCT Ser GCC Ala 565	ATA Ile 550 GTC Val	Gln 535 ATG Met TCC Ser	CCT Pro GAG Glu ATC Ile	CAC His TGC Cys	AAC Asn AAA Lys 570	GTG Val 555 GGA Gly	Gly 540 TCC Ser CTT Leu	GAA Glu TAC Tyr ATG Met	CCC Pro	AAA Lys AAA Lys 575	TCC Ser 560 CAG Gln	1680 1728
	Tyr GAA Glu 545 TTG Leu	Glu 530 CTG Leu TCC Ser	TTT Phe AAG Lys	CAG Gln GAA Glu	TCT Ser GCC Ala 565	ATA Ile 550 GTC Val	Gln 535 ATG Met TCC ser	CCT Pro GAG Glu ATC Ile	CAC His TGC Cys	AAC Asn AAA Lys 570 GAG	GTG Val 555 GGA Gly	Gly 540 TCC Ser CTT Leu	GAA Glu TAC Tyr ATG Met	CCC Pro	AAA Lys AAA Lys 575	TCC Ser 560 CAG Gln	1680
45	Tyr GAA Glu 545 TTG Leu	Glu 530 CTG Leu TCC Ser	TTT Phe AAG Lys	CAG Gln GAA Glu	TCT Ser GCC Ala 565 CTG Leu	ATA Ile 550 GTC Val	Gln 535 ATG Met TCC ser	CCT Pro GAG Glu ATC Ile	CAC His TGC Cys	AAC Asn AAA Lys 570 GAG Glu	GTG Val 555 GGA Gly	Gly 540 TCC Ser CTT Leu	GAA Glu TAC Tyr ATG Met	CCC Pro	AAA Lys AAA Lys 575 GTC Val	TCC Ser 560 CAG Gln	1680 1728
45	GAA Glu 545 TTG Leu CCT Pro	Glu 530 CTG Leu TCC Ser	TTT Phe AAG Lys AAG	CAG Gln GAA Glu CGA Arg 580	TCT Ser GCC Ala 565 CTG Leu	Gly ATA Ile 550 GTC Val	Gln 535 ATG Met TCC ser TGC Cys	CCT Pro GAG Glu ATC Ile GGG Gly	CAC His TGC Cys CCC Pro 585	AAC Asn AAA Lys 570 GAG Glu	GTG Val 555 GGA Gly GGA Gly	Gly 540 TCC ser CTT Leu GAG Glu	GAA Glu TAC Tyr ATG Met	CCC Pro ACC Thr GAT Asp	AAA Lys AAA Lys 575 GTC Val	TCC Ser 560 CAG Gln AGA Arg	1680 1728 1776
45	GAA Glu 545 TTG Leu CCT Pro	Glu 530 CTG Leu TCC Ser GCC Ala	TTT Phe  AAG Lys  AAG Lys	CAG Gln GAA Glu CGA Arg 580	TCT Ser GCC Ala 565 CTG Leu	Gly ATA Ile 550 GTC Val GGC Gly	Gln 535 ATG Met TCC ser TGC Cys	CCT Pro GAG Glu ATC Ile GGG Gly	CAC His TGC Cys CCC Pro 585	AAC Asn AAA Lys 570 GAG Glu	GTG Val 555 GGA Gly GGA Gly	Gly 540 TCC Ser CTT Leu GAG Glu	GAA Glu TAC Tyr ATG Met AGG Arg	CCC Pro ACC Thr GAT Asp 590	AAA Lys AAA Lys 575 GTC Val	TCC Ser 560 CAG Gln	1680 1728

												GGC Gly 620			_		1872
5																	
												GTC					1920
		Phe	Asp	Lys	Phe		Thr	Arg	Gly	Gln		Val	Leu	Thr	Pro		
	625					630					635					640	
40	a » m	CAC	CTC	CTC	תיים א	CCT	7 7 C	D. TT: D	CAC	~~~	m/cm	GAT	புரு	ממס	ccc	ጥጥር	1968
10												Asp					1500
•	Map	GIII	пси	Val	645	ALG	Abii	110	vob	650	DCI	тор	1110	014	655	1110	
	TCG	TAT	GTC	AAC	CCC	CAG	TTT	GTG	CAC	CCA	ATC	TTG	CAA	AGT	GCA	GTA	2016
15	Ser	Tyr	Val	Asn	Pro	Gln	Phe	Val	His	Pro	Ile	Leu	Gln	Ser	Ala	Val	
				660					665					670			
		•												·			
												ACT					2064
	Gly	Arg		Met	Ser	Lys	Gly		Glu	Leu	Phe	Thr		Val	Val	Pro	
20	•		675					680					685				
	א נוויון ע	مليم	CTT	CVV	מידים	CAT	GGC	CAT	CTT	ייממ	GGG	CAA	מממ	بالبلا	тСт	GTT	2112
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25	-				•												
	AGT	GGA	GAG	GGT	GAA	GGT	GAT	GCA	ACA	TAC	GGA	AAA	CTT	ACC	CTT	AAA	2160
	Ser	Gly	Glu	Gly	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu	Lys	
	705					710					715					720	
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30												TGG				-	2208
	Pne	116	Сув	inr	725	GIĀ	гув	Leu	PIO	730	PIO	Trp	PIO	1111	735	Vai	
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	ACT	ACT	CTC	ACT	TAT	GGT	GTT	CAA	TGC	TTT	TCT	AGA	TAC	CCA	GAT	CAT	2256
35												Arg					
				740	_	_			745					750			
												•					
												CCC					2304
	Met	Lys		His	Asp	Phe	Phe		Ser	Ala	Met	Pro		Gly	Tyr	Vai	
40			755					760					765				•
	CAC	מ אים	אפא	አ ርጥ	אידיא	ششاش	<b>ጥአ</b> ሮ	ממה	CAT	GNC	ccc	AAC	TAC	λλG	ACA	ССТ	2352
												Asn					2332
		770	**** 9	****			775	2,0	r.op	1105		780	-1-	-1-		5	
45																	
	GCT	GAA	GTC	AAG	TTT	GAA	GGT	GAT	ACC	CTT	GTT	AAT	AGA	ATC	GAG	TTA	2400
	Ala	Glu	Val	Lys	Phe	Glu	Gly	Asp	Thr	Leu	Val	Asn	Arg	Ile	Glu	Leu	
	785					790					795					800	
														_			
50												CTT		_			2448
	Lys	Gly	Ile	Asp		ГÄг	Glu	Asp	Gly		Ile	Leu	Gly	His		met	
					805					810					815		
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55												Met				_	
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-		AAT Asn															2544
5																	
	GGA	AGC	GTT	CAA	TTA	GCA	GAC	CAT	TAT	CAA	CAA	AAT	ACT	CCA	ATT	GGC	2592
	Glv	Ser	Val	Gln	Leu	Ala	Asp	His	Tvr	Gln	Gln	Asn	Thr	Pro	Ile	Gly	
	1	850					855		-2-			860				•	
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10		GGC	•														2040
	Asp	Gly	Pro	Val	Leu		Pro	Asp	Asn	His	-	Leu	ser	Thr	GIN		
	865					870					875					880	
																	•
	GCC	CTT	TCC	AAA	GAT	CCC	AAC	GAA	AAG	AGA	GAT	CAC	ATG	ATC	CTT	CTT	2688
15	Ala	Leu	Ser	Lys	qaA	Pro	Asn	Glu	Lys	Arq	qaA	His	Met	Ile	Leu	Leu	
				-	885				•	890	-				895		
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	CNC	TTT	CTA	がつれ	CCT	CCT	aga	ייייי ע	א כי א	CAT	GGG	አጥር	CAT	CVV	СТД	тъС	2736
																	2,50
	GIU	Phe	vai		Ala	AIA	GIY	TIE		HIS	GIY	Mec	Asp			TÄT	
20				900					905					910	•		
	AAA	CCT	CAG	GAG	TAA												2751
	Lys	Pro	Gln	Glu													
			915		*												
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40	Met	Ala	Asp	Val	Tyr	Pro	Ala	naA	qaA	Ser	Thr	Ala	Ser	Gin		vaı	
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	Ala	Asn	Arg	Phe	Ala	Arg	Lys	Gly	Ala	Leu	Arg	Gln	Lys	Asn	Val	His	
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	Glu	Val	Lvs	Asp	His	īvs	Phe	Tle	Ala	Ara	Phe	Phe	Lvs	Gln	Pro	Thr	
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	Pne	_	ser	HIS	Cys	The	_	Pne	TIE	Trp	GIY		GTĀ	пув	GIII	Gly	
		50					55					60		_	1		
•	Phe	Gln	Cys	Gln	Val	Cys	Cys	Phe	Val	Val	His	Lys	Arg	Cys	His	Glu	
	65					70					75					80	
50	Phe	Val	Thr	Phe	Ser	Cys	Pro	Gly	Ala	Asp	Lys	Gly	Pro	Asp	Thr	Asp	
					85	•		-		90	•	•		•	95		
	Aer	Dro	D~~	Ser		Hie	Tare	Dhe	Lare		ніс	Thr	ጥኒንዮ	Glv		Pro	
	veħ	110	~~9		~y5	*****	-y o	F 116	105	110	****		- I -	110			
	en'.	<b>53</b>	<b></b>	100	77.5	Or	<b>~</b> 1.	α.		<b>.</b>	m	<b>01.</b>				. cl-	
	Inr	rne		Asp	uis	cys	σιγ			nen	TAL	оту	•		בות	Gln	
55			115					120					125				
	Gly	Met	Lys	Cys	Asp	Thr	Cys	Asp	Met	Asn	Val	His	Asn	Gln	Cys	: Val	

		130					135					140				
	Ile 145	Asn	Asp	Pro	Ser	Leu 150	Cys	Gly	Met	Asp	His 155	Thr	Glu	Lys	Arg	Gly 160
5	Arg	Ile	Tyr	Leu	Lys 165	Ala	Glu	Val	Thr	Asp 170	Glu	Lys	Leu	His	Val 175	Thr
		_	_	180					185					Gly 190		
	-		195				-	200					205	Asn		
10	_	210			_		215					220		Gln		
	225					230		-			235	_	_	Arg		240
15			•		245					250				Asp	255	
	-			260					265					270 Tyr		
20	<del>-</del>		275					280					285	Arg		
		290					295					300		Ile		
	305					310					315			Val		320
25	Thr	Asp	Phe	Asn	325 Phe	Leu	Met	Val	Leu	330 Gly	Lys	Gly	Ser	Phe	335 Gly	Lys
	Val	Met	Leu	340 Ala	Asp	Arg	Lys		345 Thr	Glu	Glu	Leu		350 Ala	Ile	Lys
30	Ile		355 Lys	Lys	Asp	Val		360 Ile	Gln	Asp	Asp		365 Val	Glu	Cys	Thr
		370 Val	Glu	Lys	Arg	Val 390	375 Leu	Ala	Leu	Leu	Asp 395	380 380	Pro	Pro	Phe	Leu 400
35	385 Thr	Gln	Leu	His	Ser 405		Phe	Gln	Thr	Val 410	Asp	Arg	Leu	Tyr	Phe	
00	Met	Glu	Tyr	Val 420		Gly	Gly	Asp	Leu 425	Met		His	Ile	Gln 430		Val
	Gly	-		Lys					Val	Phe	Tyr		Ala 445	Glu	Ile	Ser
40	Ile	Gly 450	Leu	Phe	Phe	Leu	His 455	Lys	Arg	Gly	Ile	Ile 460	Tyr	Arg	Asp	Leu
	465					470					475					Ala 480
45					485					490					495	
				500					505					510		Tyr
			515					520					525			Leu
50	-	530					535					540	1			Asp
	545					550					555					Ser 560 Gln
55			_		565					570	)				575	
			_, _			1	~, ~	1			- 1					

				580					585					590		
	Glu	His	Ala 595		Phe	Arg	Arg	Ile 600		Trp	Glu	Lys	Leu 605		Asn	Arg
5	Glu	Ile 610	Gln	Pro	Pro	Phe	Lys 615		Lys	Val	Сув	Gly 620		Gly	Ala	Glu
J	Asn 625		Asp	Lys	Phe	Phe 630		Arg	Gly	Gln	Pro 635	Val	Leu	Thr	Pro	Pro 640
·		Gln	Leu	Val	Ile 645	Ala	Asn	Ile	Asp	Gln 650	Ser	Asp	Phe	Glu	Gly 655	Phe
10		_	Val	660					665					670		
	-		Ala 675					680					685			
15		690					695					700				
	705	_	Glu			710					715		_			720
••			Cys		725	٠				730					735	
20			Leu	740	_	_			745	•				750		
		_	Gln 755 Arg		_			760					765			
25		770	Val				775					780				
	785		Ile	_		790		_			795					800
20	=		Asn		805					810					815	
30			Gly	820					825					830		
	_		835 Val					840					845			
35		850	Pro				855					860				
	865		Ser			870					875					880
40			Val		885					890					895	
			Gln	900			,		905		•		-	910		
			915	\ <del></del>	T0714		N 70	D 65	0 TD	NO.	74.					
45			(2				N FO				/4:					
		(		LEN	GTH:	215	ACTE 7 ba ic a	se p								
50			(C)				S: s		.e			•				

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

55

(A) NAME/KEY: Coding Sequence

(B) LOCATION: 1...2154

(D) OTHER INFORMATION:

			ι ,															
5		()	ci) S	EQUE	ENCE	DESC	RIPT	: NOI	SEÇ	ID.	NO: 7	74:						
J	ATG	TCG	TCC	ATC	TTG	CCA	TTC	ACG	CCG	CCA	GTT	GTG	AAG	AGA	CTG	CTG	4	8
	Met 1	Ser	Ser	Ile	Leu 5	Pro	Phe	Thr	Pro	Pro	Val	Val	Lys	Arg	Leu 15	Leu		
10	GGA	TGG	AAG	AAG	TCA	GCT	GGT	GGG	TCT	GGA	GGA	GCA	GGC	GGA	GGA	GAG	9	6
	Gly	Trp	Lys	Lys 20	Ser	Ala	Gly	Gly	Ser 25	Gly	Gly	Ala	Gly	Gly 30	Gly	Glu		
												GCA					14	4
15	Gln	Asn	Gly 35	Gln	Glu	Glu	Lys	Trp 40	Сув	Glu	Lys	Ala	Val 45	Lys	Ser	Leu		
												GAG					19	2
20	Val	Lys 50	Lys	Leu	Lys	Lys	Thr 55	Gly	Arg	Leu	Asp	Glu 60	Leu	Glu	Lys	Ala		
												ACC					24	0
	Ile 65	Thr	Thr	Gln	Asn	Cys 70	Asn	Thr	Lys	Cys	Val 75	Thr	Ile	Pro	Ser	Thr 80		
25	maa	·mæm	C 2 2 2	y coco	TCC	CCA	CTC	אכייי	7 C7	CCA	יויי א	ACG	מידית	CNT	CNG	TCC	28	В
												Thr			_		20	
	- 4				85	-				90					95			
30												ACC					33	6
	Asp	Thr	Thr	Gly 100	Leu	Tyr	Ser	Phe	Ser 105	Glu	Gln	Thr	Arg	Ser 110	Leu	Asp		
	GGT	CGT	CTC	CAG	GTA	TCC	CAT	CGA	AAA	GGA	TTG	CCA	CAT	GTT	ATA	TAT	38	4
35	Gly	Arg	Leu 115	Gln	Val	Ser	His	Arg 120	Lys	Gly	Leu	Pro	His 125	Val	Ile	Tyr		
	TGC	CGA	TTA	TGG	CGC	TGG	CCT	GAT	CTT	CAC	AGT	CAT	CAT	GAA	CTC	AAG	43	2
40	Cys	Arg 130	Leu	Trp	Arg	Trp	Pro 135	Asp	Leu	His	Ser	His 140	His	Glu	Leu	Lys		
		» mm	~~~	7 7 C	maa	C 2 2 2	m a m	CCT	mmm	א א תר		AAA	אמכ	CINT	GNA	GT'A	48	30
												Lys					40	, ,
	145				•	150	-				155	_	_	_		160		
45	mam	CITI N	n n 🗸	COM	ma c	an a	mam	CNC	707	C III III	CNC	ACA	CCN	Cum	ጥጥር	CCT	52	a a
												Thr					<i></i>	- 0
	<b>-</b> 7-				165		-,-		3	170					175			
50																CCT	57	76
	Pro	Val	Leu	Val ·180	Pro	Arg	His	Thr	Glu 185		Leu	Thr	Glu	Leu 190		Pro		
																GCA	62	24
55	Leu	Asp	Asp	Tyr	Thr	His	Ser	Ile	Pro	Glu	Asn	Thr	Asn	Phe	Pro	Ala		

205

200

	GGA	ATT	GAG	CCA	CAG	AGT	AAT	TAT	ATT	CCA	GAA	ACG	CCA	CCT	CCT	GGA	672
												Thr 220				_	
5	m a m	አጥሮ	אכיתי	ממט	ריאידי	CCA	ממס	ת כי ת	አርተጥ	CAC	ממים	CAG	mmCi	ייית א	C	አርጥ ·	720
												Gln					720
	225					230					235					240	
10	ATG	GAC	ACA	GGC	тст	CCA	GCA	GAA	CTA	тст	ССТ	ACT	ACT	CTT	TCC	CCT	768
. •												Thr					
					245					250	•				255		
	GTT	AAT	CAT	AGC	TTG	GAT	ATT	CAG	CCA	GTT	ACT	TAC	TCA	GAA	CCT	GCA	816
15	Val	Asn	His		Leu	qaA	Leu	Gln		Val	Thr	Tyr	Ser		Pro	Ala	
				260					265					270			
												CAG					864
00	Phe	Trp	_	Ser	Ile	Ala	Tyr	_	Glu	Leu	Asn	Gln		Val	Gly	Glu	
20			275					280					285				
												GAT					912
	Thr	Phe 290	His	Ala	Ser	Gln		Ser	Leu	Thr	Val	Asp 300	Gly	Phe	Thr	Asp	
25		290					295					300				•	
												CTC					960
		Ser	Asn	Ser	Glu	-	Phe	Cys	Leu	Gly		Leu	Ser	Asn	Val	Asn 320	
	305					310					315					320	
30												ATA					1008
	Arg	Asn	Ala	Thr		Glu	Met	Thr	Arg		His	Ile	Gly	Arg		Val	
					325					330					335		
															•	GAT	1056
35	Arg	Leu	Tyr	Tyr 340	Ile	Gly	Gly	Glu	Val 345	Phe	Ala	Glu	Cys	Leu 350	Ser	Asp	
				340					343					330			
												CAG			_		1104
40	Ser	Ala	355	Phe	Val	Gin	Ser	Pro 360	Asn	Cys	Asn	Gln	Arg	Tyr	GIY	Trp	
40			555					300					505				
												TGT					1152
	His	Pro 370	Ala	Thr	Val	Cys	Lys 375	Ile	Pro	Pro	Gly	Cys 380	Asn	Leu	Lys	Ile	
45		370					3/5					30,0				•	
												CAG					1200
		Asn	Asn	Gln	Glu		Ala	Ala	Leu	Leu		Gln	Ser	Val	Asn		
	385					390			•		395					400	
50												TGC					1248
	Gly	Phe	Glu	Ala		Tyr	Gln	Leu	Thr	_	Met	Cys	Thr	Ile		Met	
					405					410					415		
	AGT	TTT	GTG	AAA	GGG	TGG	GGA	GCA	GAA	TAC	CGA	AGG	CAG	ACG	GTA	ACA	1296
55	Ser	Phe	Val	_	Gly	Trp	Gly	Ala		Tyr	Arg	Arg	Gln			Thr	
				420					425					430			

	 		TGC Cys					 						1344
5		435					440			٠	445			
			GTA Val											1392
10			TGG Trp											1440
15	 		GGC Gly										_	1488
20	 		GGC Gly 500	Asp	-	_		 						1536
0.5			GAT Asp											1584
25			AAG Lys											1632
30	 		GTG Val										_	1680
35	 		TTC											1728
40			TTC Phe 580										GTG Val	1776
			GGC Gly										ATC Ile	1824
45													AAC Asn	1872
50													GGC Gly 640	1920
55									Ile				GTG Val	1968

		CTC Leu															2016
5																	
		CTG															2064
	Val	Leu		Pro	Asp	Asn	His		Leu	Ser	Thr			Ala	Leu	Ser	
			675					680			,		685				
40		a . a	000	220	a.a		000	O. T. T.	- C - C	3 mg	000	ama	O.T.O.	an a	mma	OTC.	2112
10		GÀC Asp															2112
	гур	690	PIO	WPII	Giu	nys	695	Asp	птэ	Mec	vai	700	пеп	GIU	FIIC	Val	
		0,50					0,5					, , ,					
	ACC	GCC	GCC	GGG	ATC	ACT	CTC	GGC	ATG	GAC	GAG	CTG	TAC	AAG	TAA		2157
15	Thr	Ala	Ala	Gly	Ile	Thr	Leu	Gly	Met	Asp	Glu	Leu	Tyr	Lys			
	705					710					715				•		
											_						
			(2)	INE	ORM	ATION	1 FOI	R SE	O ID	NO:7	75:						
20		13	: \	EQUEN	7010 <i>(</i>	י כו מנור	COPI	) T Cm									
			•	LENC										•			
				TYPE					J. 40							•	
•				STRA					•								
25				TOPO				_					•				•
			٠							•							
				MOLE			-										
		(7	J) FI	RAGMI	ENT :	TYPE	: in	terna	al								
20		/-	-21	25011	-21017	DEC	7D T D1	TT ON		0 TD	NO.	7E.					
30		()	(1)	SEQUE	SNCE	וכפת	LRIP.	LTON	: 55	עו ט	NO:	, , ,					
	Met	Ser	Ser	Ile	Leu	Pro	Phe	Thr	Pro	Pro	Val	Val	Lvs	Arq	Leu	Leu	
	1		552		5					10			-1 -		15		
	Gly	Trp	Lys	Lys	Ser	Ala	Gly	Gly	Ser	Gly	Gly	Ala	Gly	Gly	Gly	Glu	
35	-	-	_	20			-	_	25	_				30			
	Gln	Asn	Gly	Gln	Glu	Glu	Lys	Trp	Cys	Glu	Lys	Ala	Val	Lys	Ser	Leu	
			35					40				_	45				
	Val	Lys	Lys	Leu	Lys	Lys		Gly	Arg	Leu	Asp		Leu	Glu	Lys	Ala	
40		50	_,		_	_	55	_,	_	_		60	<b>71</b> -	D	O	mb	
40		Thr	Thr	GIn	Asn		Asn	Thr	гЛs	Cys		Thr	TIE	Pro	Ser	80	
	65 Cv.	Co*	al.	Tla	Tro	70	T.em	802	Thr	Dro	75 Nen	Thr	Tle	Δen	Gln	Trp	
	Сув	Sei	GIU	116	85	GIY	nea	Ser	1111	90	ASII	1111	116	vob	95	115	
•	Asp	Thr	Thr	Glv		Tvr	Ser	Phe	Ser		Gln	Thr	Ara	Ser		Asp	
45				100		-1-			105					110		-	
	Gly	Arg	Leu	Gln	Val	Ser	His	Arg	Lys	Gly	Leu	Pro	His	Val	Ile	Tyr	•
	-	_	115					120	_	_			125				
	Cys	Arg	Leu	Trp	Arg	Trp	Pro	Asp	Leu	His	Ser	His	His	Glu	Leu	Lys	
		130			•		135					140				<b>-</b>	
50			Glu	Asn	Сув			Ala	Phe	Asn			Lys	Asp	Glu	Val	
	145			D	<b>m</b>	150		<b>63</b>			155		D	17-7	T 011	160 Pro	
	cys	vaı	ASD	PLO	19r 165	uls	ıyr	GIN	arg		GII	rnr	PEO	val	175	Pro	
	Dro	Wal	T,611	17 = 1		Δνα	Hie	Thr	ر، ای	170	T.211	<b>ጥ</b> ከተ	Glu	[]eli		Pro	
55	FIO	vaı	neu	180	-10	21.3		1111	185		Tea	- 11· ±	O±u	190			
55	Leu	Asp	Asp		Thr	His	Ser	Ile			Asn	Thr	Asn			Ala	
			-	•			_										

			195					200					205			
	Gly	Ile	Glu	Pro	Gln	Ser	Asn	Tyr	Ile	Pro	Glu	Thr	Pro	Pro	Pro	Gly
	-	210					215	-				220				•
	ጥኒያም	Tle	Ser	Glu	Δen	Glv	Glu	Thr	Ser	Acn	Gln		T.611	Acn	Gln	Ser
_		110	501	014	nop.		014	****	JCI	vob		GTII	пец	ASII	0111	
5	225	_			_	230			_	_	235			_	_	240
	Met	Asp	Thr	Gly	Ser	Pro	Ala	Glu	Leu	Ser	Pro	Thr	Thr	Leu		Pro
					245			-		250					255	
·	Val	Asn	His	Ser	Leu	Asp	Leu	Gln	Pro	Val	Thr	Tyr	Ser	Glu	Pro	Ala
				260		-			265			•		270		
10	Dho	Trn	Cve		TIA	λla	Tyr	Т: г>		T 611	700	C1 n	7.~~		Clv	Glu.
10	Pile	тър	_	SEL	TTE	AId	IYI	_	GIU	neu	Asii	GIII	_	vaı	GIY	GIU
	•		275	_		_		280					285			
	Thr	Phe	His	Ala	Ser	Gln	Pro	Ser	Leu	Thr	Val	Asp	Gly	Phe	Thr	Asp
		290					295					300				
	Pro	Ser	Asn	Ser	Glu	Arg	Phe	Cys	Leu	Gly	Leu	Leu	Ser	Asn	Val	Asn
15	305					310	•	-		-	315					320
		Agn	Δla	Thr		,	Met	Thr	Ara	Ara		Tla	Gly	Δνα	Glv	
	Arg	A311	AIU	1111		OIU	MCC	1111	AL 9		1115	116	Gry	ALG		Vai
			_	_	325					330	_	_			335	
	Arg	Leu	Tyr	Tyr	Ile	GIA	Gly	Glu	Val	Phe	Ala	Glu	Cys	Leu	Ser	qaA
				340					345					350		
20	Ser	Ala	Ile	Phe	Val	Gln	Ser	Pro	Asn	Cys	Asn	Gln	Arg	Tyr	Gly	Trp
			355		•			360		-			365	-	-	-
	uio	Dro		Thr	17 - 7	Cvc	Lys		D×o	Dro	C111	Crea		Len	Larg	Tla
	птв		AIG	1111	Vai	Cys		116	PIO	FIU	GIY		MSII	шец	Буб	116
	_	370					375	_			_	380			_	
	Phe	Asn	Asn	Gln	Glu	Phe	Ala	Ala	Leu	Leu	Ala	Gln	Ser	Val	Asn	Gln
25	385					390					395					400
	Gly	Phe	Glu	Ala	Val	Tyr	Gln	Leu	Thr	Arq	Met	Cys	Thr	Ile	Arg	Met
	•				405	_				410		•			415	
	Car	Dhe	Val	Lve		Trn	Gly	λla	Gl 11		7~~	7~~	Gln	Thr		Thr
	261	PIIC	var		GIY	пр	Gry	Ala		TAT	Arg	Arg	GIII		Vai	1111
	_			420	_			_	425	_	_		_	430		_
30	Ser	Thr	Pro	Cys	Trp	Ile	Glu	Leu	His	Leu	Asn	Gly	Pro	Leu	GIn	Trp
			435					440					445			
	Leu	Asp	Lys	Val	Leu	Thr	Gln	Met	Gly	Ser	Pro	Ser	Val	Arg	Cys	Ser
		450					455		_			460				
	Ser	Met	Ser	Tro	Val	Pro	Arg	Ala	Ara	Asp	Pro	Pro	Val	Ala	Thr	Met
35	465			F		470	9		5		475					480
30		<b>a</b>	*	<b>01.</b> -				<b>5</b> 1	m1	<b>01</b>		*** 7		<b>T</b> 1-	T	
	vai	Sei	гλя	GIA		GIU	Leu	Pne	THE	_	vai	vaı	PIO	116		vai
					485					490					495	
	Glu	Leu	Asp	Gly	Asp	Val	Asn	Gly	His	Lys	Phe	Ser	Val	Ser	Gly	Glu
				500					505	*				510		
40	Glv	Glu	Glv	Asp	Ala	Thr	Tyr	Glv	Lvs	Leu	Thr	Leu	Lvs	Phe	Ile	Cvs
	1		515	- L			- 4	520	-1-				525			-
	m\	77)h ee		T	T	D	11-7			D	mla aa	T			mb	T
	Thr		GIY	гав	Leu	PIO	Val	Pro	Trp	Pro	Thr		vai	THE	THE	Leu
		530					535					540				
	Thr	Tyr	Gly	Val	Gln	Cys	Phe	Ser	Arg	Tyr	Pro	Asp	His	Met	Lys	Gln
45	545					550					555					560
	His	Asp	Phe	Phe	Lvs	Ser	Ala	Met	Pro	Glu	Glv	Tvr	Val	Gln	Glu	Arg
		F			565					570		-1-			575	3
	<b>5</b> 11	<b>-1</b> -	Db -	D1		3	<b>-</b>	<b>~</b> 3	<b>-</b>		•	m\	3	77-		37-7
*	inr	TIE	Pne		гув	Asp	Asp	GIA		Tyr	гÀг	Thr	Arg		GIU	vai
				580					585					590		
50	Lys	Phe	Glu	Gly	Asp	Thr	Leu	Val	Asn	Arg	Ile	Glu	Leu	Lys	Gly	Ile
	-		595					600		_			605			
	Aen	Phe			Asn	Glv	Asn		Len	Glv	Hic	Lve		Glu	Tvr	Asn
	p		_, •			1			<u> </u>	U L Y	*****			J_ u	-1-	
	-	610	0	77-2	<b>3</b>	17-7	615	<b>-</b> 7	10 -		•	620		<b>T</b>	7	<b>01</b> -
	-	ASN	ser	HIS	Asn		Tyr	TIE	met	Ala	_	πÃ'R	GIN	гÀг	ASN	
55	625					630					635					640
	Ile	Lys	Val	Asn	Phe	Lys	Ile	Arg	His	Asn	Ile	Glu	Asp	Gly	Ser	Val
		-				-		_					_	-		

										112								
					645					650					655			
	Gln	Leu	Ala	Asp 660	His	Tyr	Gln	Gln	Asn 665		Pro	Ile	Gly	Asp 670		Pro		
5	Val	Leu	Leu 675		Asp	Asn	His	Tyr 680		Ser	Thr	Gln	Ser 685	Ala	Leu	Ser		
	Lys	Asp 690		Asn	Glu	Lys	Arg		His	Met	Val	Leu 700			Phe	Val		
	Thr	Ala	Ala	Gly	Ile	Thr 710		Gly	Met	Asp	Glu 715		Tyr	Lys				
10	,		(2)	INI	FORM		1 FOI	R SEC	) ID	NO:								
		( :		EQUE														
15			(A) (B)	LENC TYPE STR	GTH: E: nu	2397 iclei	7 bas	se pa	airs									
			(D)	TOPO	OLOGY	7: li	inear	ר										
20				OLE FEAT		TYPI	E: cI	ONA	٠				*					
			(A)	NAI	ME/KI	EY: (	Codir	ng Se	equei	nce							•	
				LOC												٠.		
25		(2	ki) S	SEQUI	ENCE	DESC	CRIP	rion	: SE	Q ID	NO:	76:						
		GAC Asp															48	
30	1				5					10				<u>-</u> -	15	-1-		
		AGC Ser															96	
35				20					25		• 5		,	30				
		ACA Thr															144	
	020		35		-1-	5		40					45	-1 -		-2 -	٠	
40		AAA Lys															192	
	011	50	-1-				55	502				60						
45		GCT Ala															240	
,	65					70	0,2				75	3				80		
		CTT Leu	_	_										_		_	288	
50	Arg	Deu	0211		85	Cly	9	טעם	Cry	90	,110	1115	·uz	110	95			
		CTC													_		336	
55	wrd	Leu	TTP	100	ττb	FIO	vah	TC (1	105	пÀр	uail	GIU	neu	110	1110	<b>* Q 1</b>		
ออ	AAA	TAT	TGT	CAG	TAT	GCG	TTT	GAC	TTA	AAA	TGT	GAT	AGT	GTC	TGT	GTG	384	470
																		172

																	•	
	Lys	Tyr	Cys 115	Gln	Tyr	Ala	Phe	Asp 120	Leu	Lys	Сув	Asp	Ser 125	V _a l	Cys	Val		
5	AAT Asn	CCA Pro 130	TAT Tyr	CAC His	TAC Tyr	GAA Glu	CGA Arg 135	GTT Val	GTA Val	TCA Ser	CCT Pro	GGA Gly 140	ATT Ile	GAT Asp	CTC Leu	TCA Ser	432	
10										Ser			ATG Met				480	
	GAA Glu	TAT Tyr	GTG Val	CAT His	GAC Asp 165	TTT Phe	GAG Glu	GGA Gly	CAG Gln	CCA Pro 170	TCG Ser	TTG Leu	TCC Ser	ACT Thr	GAA Glu 175	GGA Gly	528	
15													CGT Arg				576	
20	GAG Glu	ACA Thr	TAC Tyr 195	AGC Ser	ACC	CCA Pro	GCT Ala	CTG Leu 200	TTA Leu	GCC Ala	CCA Pro	TCT Ser	GAG Glu 205	TCT Ser	AAT Asn	GCT Ala	624	
25	ACC Thr	AGC Ser 210	Thr	GCC Ala	AAC Asn	TTT Phe	CCC Pro 215	AAC Asn	ATT Ile	CCT Pro	GTG Val	GCT Ala 220	TCC Ser	ACA Thr	AGT Ser	CAG Gln	672	
30	CCT Pro 225	GCC Ala	AGT Ser	ATA Ile	CTG Leu	GGG Gly 230	GGC Gly	AGC Ser	CAT	AGT Ser	GAA Glu 235	GGA Gly	CTG Leu	TTG Leu	CAG Gln	ATA Ile 240	720	
	GCA Ala	TCA Ser	GGG Gly	CCT Pro	CAG Gln 245	Pro	GGA Gly	CAG Gln	CAG Gln	CAG Gln 250	AAT Asn	GGA Gly	TTT Phe	ACT	GGT Gly 255	CAG Gln	768	
35	CCA Pro	GCT Ala	ACT Thr	TAC Tyr 260	His	CAT His	AAC Asn	AGC Ser	ACT Thr 265	Thr	ACC Thr	TGG Trp	ACT Thr	GGA Gly 270	AGT	AGG Arg	816	
40	ACT Thr	GCA Ala	CCA Pro 275	Tyr	ACA Thr	CCT	raa '	TTC Lev 280	Pro	CAC His	CAC His	CAA Glr	AAC Asn 285	Gly	CAT His	CTT Leu	864	
45	CAG Gln	CAC His	His	CCG	CCI Pro	ATG Met	CCC Pro 295	Pro	CAT His	CCC Pro	GGA Gly	CAT His	Tyr	TGG	CCI Pro	GTT Val	912	
50	CAC His	Asr	GAG Glu	CTI Lev	GCA Ala	TTC Phe 310	Glr	G CCT	CCC Pro	TATI	TCC Ser 315	Ası	r CAT n His	CCT Pro	GCT Ala	CCT Pro 320	960	
	GAG Glu	TAT	TGG Trp	TGI Cys	TC0 Se1	c Ile	GC:	г ТА( а Ту:	TTT r Phe	GA/ ∈ Glu 330	ı Met	GA' Asj	r GT7 p Val	CAC Glr	GTI 1 Va: 33:	A GGA L Gly	1008	
55	GAC	G ACI	A TT	OAA 1	GT:	r cc:	r TC	A AG	C TG	c cc:	r ati	r gt	T AC	r GT	r GA'	r gga	1056	173

										• • •							
	Glu	Thr	Phe	Lys 340	Val	Pro	Ser	Ser	Cys 345	Pro	Ile	Val	Thr	Val 350	Asp	Gly	
	TAC	GTG	GAC	ССТ	TCT	GGA	GGA	GAT	CGC	ጥጥጥ	TGT	ттс	GGT	CAA	CTC	TCC	1104
5					Ser												
•	-1-		355			<b>υ-1</b> .	<b>-</b> -1	360	••••		0,0		365				
					٠												
	AAT	GTC	CAC	AGG	ACA	GAA	GCC	ATT	GAG	AGA	GCA	AGG	TTG	CAC	ATA	GGC	1152
	Asn	Val	His	Arg	Thr	Glu	Ala	Ile	Glu	Arg	Ala	Arg	Leu	His	Ile	Gly.	
10		370					375					380					
					TTG												1200
		Gly	Val	Gln	Leu		Cys	Lys	Gly	Glu	-	Asp	Val	Trp	Val		
45	385					390					395					400	
15	maa	COTO	א פיתי	כאכ	CAC	ccc	CTC	mmm	CTDX	CZC	7 CT	ma C	<b>ምአ</b> ሮ	ጥጥአ	CAC	אמא	1248
					His												1240
	Cys	neu	SCI	ASP	405	AIG	vai	FIIC	vai	410	261	TYL	TYT	ДСи	415	AL 9	
					105				•	410					7.20		
20	GAA	GCT	GGG	CGT	GCA	CCT	GGA	GAT	GCT	GTT	CAT	AAG	ATC	TAC	CCA	AGT	1296
					Ala												
		,	_	420	•		_	-	425			-		430			
	GCA	TAT	ATA	AAG	GTC	TTT	GAT	TTG	CGT	CAG	TGT	CAT	CGA	CAG	ATG	CAG	1344
25	Ala	Tyr	Ile	Lys	Val	Phe	Asp	Leu	Arg	Gln	Cys	His	Arg	Gln	Met	Gln	
			435					440					445				
								~~-			~~~		~~~			000	1200
					ACT									_	_	_	1392
30	GIn	450	АТА	Ala	Thr	ATA	455	АТА	Ala	АТА	Ala	460	GIN	Ala	Ala	Ala	
30		450					433					400					
	GTG	GCA	GGA	AAC	ATC	ССТ	GGC	CCA	GGA	TCA	GTA	GGT	GGA	ATA	GCT	CCA	1440
					Ile												
	465		•			470	•		_		475	•	-			480	
35														•			
	GCT	ATC	AGT	CTG	TCA	GCT	GCT	GCT	GGA	ATT	GGT	GTT	GAT	GAC	CTT	CGT	1488
	Ala	Ile	Ser	Leu	Ser	Ala	Ala	Ala	Gly	Ile	Gly	Val	Asp	Asp	Leu	Arg	
	•		•		485					490					495		
40					CTC												1536
	Arg	Leu	Cys		Leu	Arg	Met	Ser		Val	Lys	GIY	Trp		Pro	Asp	
				500					505					510			
-	ጥአሮ	CCA	AGA	CAG	AGC	ΔТС	מממ	GAA	מים	CCT	TCC	TGG	יידע	GAD	עייינע	CAC	1584
45					Ser										_	_	1001
40	-7-	110	515	<b>U</b>	DÇI	110	-75	520	* ***	110	Cyb		525				
	TTA	CAC	CGG	GCC	CTC	CAG	CTC	CTA	GÁC	GAA	GTA	CTT	CAT	ACC	ATG	CCG	1632
	Leu	His	Arg	Ala	Leu	Gln	Leu	Leu	Asp	Glu	Val	Leu	His	Thr	Met	Pro	
50		530	_				535		~			540					
					CAA										_		1680
		Ala	Asp	Pro	Gln		Leu	Asp	Trp	Asp		Pro	Val	Ala	Thr		
	545					550					555					560	
55	<b>a</b> =-			000	C 3 C	<b>~~~</b>	~~~	m= -		~~~	ama		000	3.000	~~~	CTC.	1520
	G.T.G	AGC	AAG	GGC	GAG	GAG	CIG	T.I.C.	ACC	હહહ	GTG	GIG	CCC	ATC	CIG	GIC	1728

	Val	Ser	Lys	Gly	Glu 565	Glu	Leu	Phe	Thr	Gly 570	Val	Val	Pro	Ile	Leu 575	Val	
5			GAC Asp														1776
10			GGC Gly 595														1824
15			GGC Gly														1872
13			GGC Gly														1920
20			TTC Phe														1968
25			TTC Phe														2016
30			GAG Glu 675						Asn								2064
25			AAG Lys														2112
35			AGC Ser														2160
40			GTG Val														2208
45			GCC Ala														2256
50			CTG Leu 755														2304
			CCC Pro														2352
55	ACC	GCC	GCC	GGG	ATC	ACT	CTC	GGC	ATG	GAC	GAG	CTG	TAC	AAG	TAA		2397 17

WO 98/45704 PCT/DK98/00145

176

Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys 785 790 795

5 (2) INFORMATION FOR SEQ ID NO:77:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 798 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (v) FRAGMENT TYPE: internal

15

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

	Met 1	Asp	Asn	Met	Ser 5	Ile	Thr	Asn	Thr	Pro 10	Thr	Ser	Asn	Asp	Ala 15	Cys
20	Leu	Ser	Ile	Val	His	Ser	Leu	Met	Cys 25	His	Arg	Gln	Gly	Gly	Glu	Ser
	Glu	Thr	Phe 35	Ala	Lys	Arg	Ala	Ile 40	Glu	Ser	Leu	Val	Lys 45	Lys	Leu	Lys
25	Glu	Lys 50	Lys	Asp	Glu	Leu	Asp 55	Ser	Leu	Ile	Thr	Ala 60	Ile	Thr	Thr	Asn
	Gly 65	Ala	His	Pro	Ser	Lys 70	Сув	Val	Thr	Ile	Gln 75	Arg	Thr	Leu	Asp	Gly 80
	Arg	Leu	Gln	Val	Ala 85	Gly	Arg	Lys	Gly	Phe 90	Pro	His	Val	Ile	Tyr 95	Ala
30	Arg	Leu	Trp	Arg 100	Trp	Pro	Asp	Leu	His 105	Lys	Asn	Glu	Leu	Lys 110	His	Val
	Lys	Tyr	Cys 115	Gln	Tyr	Ala	Phe	Asp 120	Leu	Lys	Cys	Asp	Ser 125	Val	Cys	Val
35	Asn	Pro 130	Tyr	His	Tyr	Glu	Arg 135	Val	Val	Ser	Pro	Gly 140	Ile	Asp	Leu	Ser
	Gly 145	Leu	Thr	Leu	Gln	Ser 150	Asn	Ala	Pro	Ser	Ser 155	Met	Met	Val	Lys	Asp 160
	Glu	Tyr	Val	His	Asp 165	Phe	Glu	Gly	Gln	Pro 170	Ser	Leu	Ser	Thr	Glu 175	_
40	His	Ser	Ile	Gln 180	Thr	Ile	Gln	His	Pro 185	Pro	Ser	Asn	Arg	Ala 190	Ser	Thr
	Glu	Thr	Tyr 195	Ser	Thr	Pro	Ala	Leu 200	Leu	Ala	Pro	Ser	Glu 205	Ser	Asn	Ala
45	Thr	Ser 210	Thr	Ala	Asn	Phe	Pro 215	Asn	Ile	Pro	Val	Ala 220	Ser	Thr	Ser	Gln
	Pro 225	Ala	Ser	Ile	Leu	Gly 230	Gly	Ser	His	Ser	Glu 235	Gly	Leu	Leu	Gln	Ile 240
	Ala	Ser	Gly	Pro	Gln 245	Pro	Gly	Gln	Gln	Gln 250	Asn	Gly	Phe	Thr	Gly 255	Gln
50	Pro	Ala	Thr	Tyr 260	His	His	Asn	Ser	Thr 265	Thr	Thr	Trp	Thr	Gly 270	Ser	Arg
	Thr	Ala	Pro 275	Tyr	Thr	Pro	Asn	Leu 280	Pro	His	His	Gln	Asn 285	Gly	His	Leu
55	Gln	His 290	His	Pro	Pro	Met	Pro 295	Pro	His	Pro	Gly	His 300	Tyr	Trp	Pro	Val
	His		Glu	Leu	Ala	Phe	Gln	Pro	Pro	Ile	Ser	Asn	His	Pro	Ala	Pro

	305					310					315					320
		Tyr	Trp	Cys			Ala	Tyr	Phe			Asp	Val	Gln	Val	
			•		325					330					335	
5	Glu	Thr	Phe	Lys 340	Val	Pro	Ser	Ser	Cys 345	Pro	Ile	Val	Thr	Val 350	Asp	Gly
	Tyr	Val	Asp 355	Pro	Ser	Gly	Gly	Asp	Arg	Phe	Cys	Leu	Gly 365	Gln	Leu	Ser
• .	Asn			Arg	Thr	Glu			Glu	Arg	Ala			His	Ile	Gly
40	_	370			_		375				_	380				
10	Lys 385	Gly	Val	Gln	Leu	Glu 390	Сув	Lys	Gly	Glu	Gly 395	Asp	Val	Trp	Val	Arg 400
	Cys	Leu	Ser	Asp	His	Ala	Val	Phe	Val	Gln 410	Ser	Tyr	Tyr	Leu	Asp 415	Arg
	Glu	Ala	Gly	Arq	Ala	Pro	Glv	Asp	Ala		His	Lvs	Ile	Tyr		Ser
15				420					425					430		
	Ald	TYL	435	- пув	vai	PHE	Asp	440	Arg	GII	Cys	HIS	445	Gln	Mec	GIN
	Gln	Gln		Δla	Thr	בומ	Gln		λla	715	7 T =	ת [ ת		Ala	λla	λl-
4	0111	450			****	AIG	455	ATA	NI a	AIG	AIG	460	GIII	AIG	міа	AIG
20	Va1		Glv	Asn	Tle	Pro		Pro	Glv	Ser	Vai		Glv	Ile	Δla	Pro
. = -	465		1		÷	470	017	110	O+1	001	475	Cry	Ory	110	niu	480
	Ala	Ile	Ser	Leu	Ser	Ala	Ala	Ala	Gly	Ile	Gly	Val	Asp	Asp	Leu	Arg
					485				-	490	•		-	-	495	_
25	Arg	Leu	Cys	Ile 500	Leu	Arg	Met	Ser	Phe 505	Val	Lys	Gly	Trp	Gly 510	Pro	qaA
	Tyr	Pro	Arg 515	Gln	Ser	Ile	Lys	Glu 520		Pro	Cys	Trp	Ile 525	Glu	Ile	His
	Leu	His		Ala	Len	Gln	Ĭ.e.11		Aen	Glu	Va l	Len		Thr	Met	Pro
	200	530	••••		200	0111	535	DCu.	waħ	Giu	vai	540	mrs	1111	Mec	FIO
30	Ile		Asp	Pro	Gln	Pro		qaA	Trp	Asp	Pro		Val	Ala	Thr	Met
	545		-			550		•	•		555					560
	Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	
					565					570					575	
35	Glu	Leu	Asp	Gly 580	Asp	Val	Asn	Gly		Lys	Phe	Ser	Val	Ser	Gly	Glu
33	Gly	Glu			Ala	Thr	Tyr		585 Lys	Leu	Thr	Leu	Lys	590 Phe	Ile	Cys
		_,	595	_	_	_		600	•				605			
	Thr	Thr 610	GIÀ	Lys	Leu	Pro	Val 615	Pro	Trp	Pro	Thr	Leu 620	Val	Thr	Thr	Leu
40	Thr	Tyr	Gly	Val	Gln	Cys	Phe	Ser	Arg	Tyr	Pro	Asp	His	Met	Lys	Gln
	625					630					635					640
	His	Asp	Phe	Phe	Lys 645	Ser	Ala	Met	Pro	Glu 650	Gly	Tyr	Val	Gln	Glu 655	Arg
45	Thr	Ile	Phe	Phe 660	Lys	Asp	Asp	Gly	Asn 665	Tyr	Lys	Thr	Arg	Ala 670	Glu	Val
.0	Lys	Phe	Glu		Asp	Thr	Leu	Val		Arq	Ile	Glu	Leu	Lys	Gly	Ile
	_		675		_			680		-			685	•	-	
	Asp	Phe 690	Lys	Glu	Asp	Gly	Asn 695	Ile	Leu	Gly	His	Lys 700	Leu	Glu	Tyr	Asn
50	Tyr 705	Asn	Ser	His	Asn	Val 710	Tyr	Ile	Met	Ala	Asp 715	Lys	Gln	Lys	Asn	Gly 720
		Lvs	Val	Asn	Phe		Tle	Ara	Hic	Aen		Glu	Aen	Gly	Ser	
					725					730					735	
55	Gln	Leu	Ala	Asp 740	His	Tyr	Gln	Gln	Asn 745	Thr.	Pro	Ile	Gly	Asp 750	Gly	Pro
	Val	Leu	Leu	Pro	Asp	Asn	His	Tyr	Leu	Ser	Thr	Gln	Ser	Ala	Leu	Ser

									7	78		•	•			•		
	Lys	Asp	755 Pro	Asn	Glu	Lys	Arg	760 Asp	His	Met	Val	Leu	765 Leu	Glu	Phe	Val		
		770		_	_		775	_				780						
5	Thr 785	Ala	Ala	Gly	Ile	Thr 790	Leu	Gly	Met	Asp	Glu 795	Leu	Tyr	Lys				
			(2)	INF	ORMA	MOIT	FOR	SEC	) ID	NO : 7	8:		,					
10		(i	(A) (B) (C)	EQUEN LENG TYPE STRA TOPO	TH: : nu NDEI	3138 clei NESS	bas c ac : si	e pa id ngle	irs									
15				OLEC		TYPE	E: c[	)NA										
20			(B)	NAM LOC	CATIC	N: J	3	135	equen	ice		•						
		()	(i) S	EQUE	ENCE	DESC	RIPT	CION:	SEC	) ID	NO: 7	78:						
25														GCG Ala			48	
30														GTC Val 30			96	
														ATT Ile			144	
35					qaA		Ala	Gln		Thr	Gln	Leu		GAG Glu			192	
40														GAA Glu		_	240	
45														CTC Leu			288	
50														CGG Arg 110			336	
55														TGC Cys		TCT Ser	·· 384	
30	CCG	GCT	GGG	ATC	CTG	GTT	GAC	GCC	ATG	TCC	CAG	AAG	CAC	CTT	CAG	ATC	432	178

	Pro	Ala 130	Gly	Ile	Leu	Val	Asp 135	Ala	Met	Ser	Gln	Lys 140	His	Leu	Gln	Ile	
5									CTG Leu								480
10									CAG Gln								528
15									CAG Gln 185								576
10		Pro							GAG Glu								624
20	-								CGT Arg								672
25									CAC His								720
30									GAT Asp								768
35									GGC Gly 265								816
33									AAG Lys								864
40									GAG Glu								912
45									CTG Leu								960
50									ACC. Thr								1008
									CAG Gln 345							_	1056
55	CGC	CTG	CTG	GTG	GGC	GGG	AAG	CTG	AAC	GTG	CAC	ATG	AAT	CCC	CĆC	CAG	1104

	Arg	Leu	Leu 355	Val	Gly	Gly	Lys	Leu 360	Asn	Val	His	Met	Asn 365	Pro	Pro	Gln	
5									CAG Gln								1152
10									AGT Ser								1200
									ACG Thr								1248
15									AAG Lys 425						_	_	1296
20									ACA Thr								1344
25									TTC Phe								1392
30 .									AGC Ser							_	1440
									GCT Ala								1488
35									CCG Pro 505								1536
40									AGC Ser							_	1584
45									CTG Leu								1632
50									GTG Val			Ser					1680
									ACC Thr								1728
55	GTG	ATG	GAG	GTG	TTG	AAG	AAG	CAC	CAC	AAG	ccc	CAC	TGG	AAT	GAT	GGG	1776

										101							
	Val	Met	Glu	Val 580	Leu	Lys	Lys	His	His 585	Lys	Pro	His	Trp	Asn 590	Asp	Gly	
5					TTT Phe												1824
10					GGG Gly												1872
15					ATC Ile												1920
15					CCA Pro 645											-	1968
20					GGG Gly												2016
25					GAG Glu									Val			2064
30					GGA Gly												2112
25					GCA Ala												2160
35					CCC Pro 725												2208
40					AAC Asn												2256
45					ACC Thr												2304
50	- "				GAC Asp			-	_						_	_	2352
					GCC Ala												2400
55	GAT	CCA	CCG	GTC	GCC	ACC	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	2448

	qaA	Pro	Pro	Val	Ala 805	Thr	Met	Val	Ser	Lys 810	Gly	Glu	Glu	Leu	Phe 815	Thr	
	GGG	GTG	GTG	כככ	אדכ	CTG	GTC	GAG	CTG	GAC	GGC	GAC	ста	ממ	GGC	CAC	2496
5															Gly		2490
J	GIY	vai	Val		116	ьец	vaı	GIU		Asp	GIY	Авр	vaı		GIY	urs	
				820					825					830			
		mmc		ama	maa	~~~	~~~				~~ -						
															GGC		2544
	ьуs	Phe			Ser	GIA	Glu	_	Glu	Gly	Asp	Ala		Tyr	Gly	Lys	
10			835	٠.				840					845				
															CCC		2592
	Leu	Thr	Leu	Lys	Phe	Ile	Cys	Thr	Thr	Gly	Lys	Leu	Pro	Val	Pro	Trp .	
		850					855					860					
15																	÷
	CCC	ACC	CTC	GTG	ACC	ACC	CTG	ACC	TAC	GGC	GTG	CAG	TGC	TTC	AGC	CGC	2640
	Pro	Thr	Leu	Val	Thr	Thr	Leu	Thr	Tyr	Gly	Val	Gln	Cys	Phe	Ser	Arg	
	865					870				_	875					880	
								*									
20	TAC	CCC	GAC	CAC	ATG	AAG	CAG	CAC	GAC	TTC	TTC	AAG	TCC	GCC	ATG	CCC	2688
															Met		
	- 4 -		•		885					890		-1-		,	895		
																	•
	AAD	GGC	TAC	GTC	CAG	GAG	CGC	ΔCC	ልጥሮ	ጥጥር	חחכ	DZG	GAC	GAC	GGC	אאכי	2736
25															Gly		2,50
20	014	OI,		900	0111	Ozu	AL 9	1111	905	FIIC	FIIC	Dy 5	тър	910	Oly	Poli	
				300					905					910			
	<b>ምአ</b> ሮ	አአር	እርር	ccc	acc	GVG	CTC	אמע	mm/C	CVC	aac	GNC	אככ	CTC	GTG	አአር	2784
																	2704
30	IYI	тув		Arg	MIG	GIU	vai	_	PHE	GIU	GIY	Авр		ьeu	Val	ASII	
30			915					920					925				
	áaa	» ma	030	ama	220	000	3 ma	a » a	mma	770	ara	~~~	000	770	n ma	ama	2022
															ATC		2832
	Arg		GIU	Leu	ràs	GIA		Asp	Pne	ьув	GIU		GIA	Asn	Ile	Leu	
25		930					935					940					
35		~			~~~												
															ATC		2880
	_	HIS	гàв	Leu	GIU	_	Asn	Tyr	Asn	ser		Asn	vaı	Tyr	Ile		
	945					950					955					960	
40																	
40															CGC		2928
	Ala	Asp	Lys	Gln	Lys	Asn	Gly	Ile	Lys	Val	Asn	Phe	Lys	Ile	Arg	His	
					965					970					975		
	AAC	ATC	GAG	GAC	GGC	AGC	GTG	CAG	CTC	GCC	GAC	CAC	TAC	CAG	CAG	AAC	2976
45	Asn	Ile	Glu	Asp	Gly	Ser	Val	Gln	Leu	Ala	Asp	His	Tyr	Gln	Gln	Asn	
				980					985					990		•	
•																	
	ACC	CCC	ATC	GGC	GAC	GGC	CCC	GTG	CTG	CTG	CCC	GAC	AAC	CAC	TAC	CTG	3024
	Thr	Pro	Ile	Gly	Asp	Gly	Pro	Val	Leu	Leu	Pro	Asp	Asn	His	Tyr	Leu	
50			995	_				1000					1005				
	AGC	ACC	CAG	TCC	GCC	CTG	AGC	ÀAA	GAC	CCC	AAC	GAG	AAG	CGC	GAT	CAC	3072
	Ser	Thr	Gln	Ser	Ala	Leu	Ser	Lys	Asp	Pro	Asn	Glu	Lys	Arg	Asp	His	
		1010					1015	•	•			1020	•	_	•		
55																	
	ATG	GTC	CTG	CTG	GAG	TTC	GTG	ACC	GCC	GCC	GGG	ATC	ACT	CTC	GGC	ATG	3120
		_	_	•			_				_						•

183

Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met 1025 1030 1035 GAC GAG CTG TAC AAG TAA 3138 Asp Glu Leu Tyr Lys 1045 (2) INFORMATION FOR SEQ ID NO:79: 10 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 1045 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 15 (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:79: Met Ala Gly Trp Ile Gln Ala Gln Gln Leu Gln Gly Asp Ala Leu Arg Gln Met Gln Val Leu Tyr Gly Gln His Phe Pro Ile Glu Val Arg His 25 Tyr Leu Ala Gln Trp Ile Glu Ser Gln Pro Trp Asp Ala Ile Asp Leu Asp Asn Pro Gln Asp Arg Ala Gln Ala Thr Gln Leu Leu Glu Gly Leu 30 Val Gln Glu Leu Gln Lys Lys Ala Glu His Gln Val Gly Glu Asp Gly 70 75 Phe Leu Leu Lys Ile Lys Leu Gly His Tyr Ala Thr Gln Leu Gln Lys Thr Tyr Asp Arg Cys Pro Leu Glu Leu Val Arg Cys Ile Arg His Ile 35 100 105 Leu Tyr Asn Glu Gln Arg Leu Val Arg Glu Ala Asn Asn Cys Ser Ser 120 Pro Ala Gly Ile Leu Val Asp Ala Met Ser Gln Lys His Leu Gln Ile 135 40 Asn Gln Thr Phe Glu Glu Leu Arg Leu Val Thr Gln Asp Thr Glu Asn 155 150 Glu Leu Lys Lys Leu Gln Gln Thr Gln Glu Tyr Phe Ile Ile Gln Tyr 170 Gln Glu Ser Leu Arg Ile Gln Ala Gln Phe Ala Gln Leu Ala Gln Leu 45 185 Ser Pro Gln Glu Arg Leu Ser Arg Glu Thr Ala Leu Gln Gln Lys Gln 200 Val Ser Leu Glu Ala Trp Leu Gln Arg Glu Ala Gln Thr Leu Gln Gln 215 220 Tyr Arg Val Glu Leu Ala Glu Lys His Gln Lys Thr Leu Gln Leu Leu 50 230 235 Arg Lys Gln Gln Thr Ile Ile Leu Asp Asp Glu Leu Ile Gln Trp Lys 250 Arg Arg Gln Gln Leu Ala Gly Asn Gly Gly Pro Pro Glu Gly Ser Leu 55 265

Asp Val Leu Gln Ser Trp Cys Glu Lys Leu Ala Glu Ile Ile Trp Gln

PCT/DK98/00145 WO 98/45704

			275					280					285			
	Asn	Arg 290	Gln	Gln	Ile	Arg	Arg 295	Ala	Glu	His	Leu	Cys 300	Gln	Gln	Leu	Pro
5	Ile 305	Pro	Gly	Pro	Val	Glu 310	Glu	Met	Leu	Ala	Glu 315	Val	Asn	Ala	Thr	Ile 320
		Asp	Ile	Ile	Ser 325	Ala	Leu	Val	Thr	Ser 330		Phe	Ile	Ile	Glu 335	Lys
	Gln	Pro	Pro	Gln 340	Val	Leu	Lys	Thr	Gln 345		Lys	Phe	Ala	Ala 350		Vạl
10	Arg	Leu	Leu 355		Gly	Gly	Lys	Leu 360		Val	His	Met	Asn 365		Pro	Gln
•	Val	Lys 370	Ala	Thr	Ile	Ile	Ser 375		Gln	Gln	Ala	Lys 380		Leu	Leu	Lys
15	Asn 385	Glu	Asn	Thr	Arg	Asn 390	Glu	Сув	Ser	Gly	Glu 395	Ile	Leu	Asn	Asn	Cys 400
		Val	Met	Glu	Tyr 405	His	Gln	Ala	Thr	Gly 410	Thr	Leu	Ser	Ala	His 415	Phe
	Arg	Asn	Met	Ser 420	Leu	Lys	Arg	Ile	Lys 425	Arg	Ala	Asp	Arg	Arg 430	Gly	Ala
20	Glu	Ser	Val 435	Thr	Glu	Glu	Lys	Phe 440	Thr	Val	Leu	Phe	Glu 445	Ser	Gln	Phe
	Ser	Val 450	Gly	Ser	Asn	Glu	Leu 455	Val	Phe	Gln	Val	Lys 460	Thr	Leu	Ser	Leu
25	Pro 465	Val	Val	Val	Ile	Val 470	His	Gly	Ser	Gln	Asp 475	His	Asn	Ala	Thr	Ala 480
	Thr	Val	Leu	Trp	Asp 485	Asn	Ala	Phe	Ala	Glu 490	Pro	Gly	Arg	Val	Pro 495	Phe
	Ala	Val	Pro	Asp 500	Гуз	Val	Leu	Trp	Pro 505	Gln	Leu	Сув	Glu	Ala 510	Leu	Asn
30	Met	Lys	Phe 515	Lys	Ala	Glu	Val	Gln 520	Ser	Asn	Arg	Gly	Leu 525	Thr	Lys	·Glu
	Asn	Leu 530	Val	Phe	Leu	Ala	Gln 535	Lys	Leu	Phe	Asn	Asn 540	Ser	Ser	Ser	His
35	Leu 545	Glu	Asp	Tyr	Ser	Gly 550	Leu	Ser	Val	Ser	Trp 555	Ser	Gln	Phe	Asn	Arg 560
	Glu	Asn	Leu	Pro	Gly 565	Trp	Asn	Tyr	Thr	Phe 570	Trp	Gln	Trp	Phe	Asp 575	Gly
	Val	Met	Glu	Val 580	Leu	Lys	Lys	His	His 585	Lys	Pro	His	Trp	Asn 590	Asp	Gly
40	Ala	Ile	Leu 595	Gly	Phe	Val	Asn	Lys	Gln	Gln	Ala	His	Asp 605	Leu	Leu	Ile
	Asn	Lys 610	Pro	Asp	Gly	Thr	Phe 615	Leu	Leu	Arg	Phe	Ser 620	Asp	Ser	Glu	Ile
45	Gly 625	Gly	Ile	Thr	Ile	Ala 630	Trp	Lys	Phe	Asp	Ser 635	Pro	Glu	Arg	Asn	Leu 640
	Trp	Asn	Leu	Lys	Pro 645	Phe	Thr	Thr	Arg	Asp 650	Phe	Ser	Ile	Arg	Ser 655	Leu
	Ala	Asp	Arg	Leu 660	Gly	Asp	Leu	Ser	Tyr 665	Leu	Ile	Tyr	Val	Phe 670	Pro	Asp
50	Arg	Pro	Lys 675	qaA	Glu	Val	Phe	Ser 680	Lys	Tyr	Tyr	Thr	Pro 685	Val	Leu	Ala
	-	Ala 690					695	_				700				
55	705	Phe				710					715					720
	Mot	Δen	aln	Δla	Pro	Ser	Dro	777	37-7	Care	Dro	Gln	λla	Dro	ጥነተን	Δen

					725					730					735		•	
	Met	Tyr	Pro	Gln 740	Asn	Pro	Asp	His	Val 745	Leu	Asp	Gln	Asp	Gly 750	Glu	Phe		
5	Asp	Leu	Asp 755	Glu	Thr	Met	Asp	Val 760	Ala	Arg	His	Val	Glu 765	Glu	Leu	Leu		
	Arg	Arg 770	Pro	Met	Asp	Ser	Leu 775	Asp	Ser	Arg	Ļeu	Ser 780	Pro	Pro	Ala	Gly	•	
·	Leu 785	Phe	Thr	Ser	Ala	Arg 790	Gly	Ser	Leu	Ser	Trp 795	Val	Pro	Arg	Ala	Arg 800		
10	Asp	Pro	Pro	Val	Ala 805	Thr	Met	Val	Ser	Lys 810	Gly	Glu	Glu	Leu	Phe 815	Thr		
	•	Val		820					825	_	_	_		830	_			
15	_	Phe	835					840					845					
		Thr 850					855	•				860						
	865	Thr				870			_	•	875		-			880		
20	-	Pro	-		885	_			_	890		-			895			
		Gly	_	900					905					910				
25	-	Lys	915	_				920					925					
	-	Ile 930					935					940						
30	945	His Asp				950					955					960		
30		Ile			965					970					975			
		Pro		980					985	·				990				
35		Thr	995	-	_	_		1000					1005					
		1010 Val					1015	_				1020						
40	025					1030										1040		
				_	1045													
			(2	) IN	FORM	ATIO	N FO	R SE	Q ID	NO:	80:							
45		(	(A)	LEN	GTH:	28	base	pai								<b>V</b>		
			(C)	TYP:	ANDE	DNES	S: s	ingl	.e									
50			(D)	TOP	OLOG	Y: l	inea	r										
		(	xi)	SEQU	ENCE	DES	CRIP	TION	I: SE	Q II	NO:	80:	•					
	TGG	GATC	CTC	AGGC	CGTG	CT G	CTGG	CCG									2	В
55			(2	) IN	FORM	ATIO	N FC	R SE	Q II	NO:	81:							465
																		185

5	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 27 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>		
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:		
	GTCTCGAGGG AGCATGGGCA CCTTGCG		27
	(2) INFORMATION FOR SEQ ID NO:82:		
15	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 27 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>		•
20			
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:		,
25	TGGGATCCGA GAAGTCTATA TCCCATC	•	27
	(2) INFORMATION FOR SEQ ID NO:83:		
30	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 28 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>		
35	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:		
	TGGGATCCTT AGAAGTCTAT ATCCCATC		28
40	(2) INFORMATION FOR SEQ ID NO:84:		
	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 28 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li></ul>		
45	(D) TOPOLOGY: linear		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:		
50	GTCTCGAGCC ATGAACGCCC CCGAGCGG		28
	(2) INFORMATION FOR SEQ ID NO:85:		•
55	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 30 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>		
			186

	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	·
5	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:	
	GTGAATTCTC GTCTGATTTC TGGCAGGAGG	30
10	(2) INFORMATION FOR SEQ ID NO:86:	
10	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 30 base pairs  (B) TYPE: nucleic acid	
15	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:	
20	GTGAATTCTT TACGTCTGAT TTCTGGCAGG	30
	(2) INFORMATION FOR SEQ ID NO:87:	
25	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 34 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
30		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:	
	GTCTCGAGCC ATGGACGAAC TGTTCCCCCT CATC	34
35	(2) INFORMATION FOR SEQ ID NO:88:	
40	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 31 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li></ul>	
	(D) TOPOLOGY: linear	
45	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:	
	GTGGATCCAA GGAGCTGATC TGACTCAGCA G	31
	(2) INFORMATION FOR SEQ ID NO:89:	
50	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 32 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
55	(D) TOPOLOGI. IIIIEAL	

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:	
	GTGGATCCTT AGGAGCTGAT CTGACTCAGC AG	32
5	(2) INFORMATION FOR SEQ ID NO:90:	
10	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 32 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
15	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:	•
15	CCTCCTAAGC TTATCATGGA CCATTATGAT TC	32
	(2) INFORMATION FOR SEQ ID NO:91:	
20	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 33 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li></ul>	
25	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:	
30	CCTCCTGGAT CCCTGCGCAG GATGATGGTC CAG  (2) INFORMATION FOR SEQ ID NO:92:	33
35	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 45 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
40	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:	
	GGATGGAAGC TTCAATGGCT GCCATCCGGA AGAAACTGGT GATTG	45
45	<ul><li>(2) INFORMATION FOR SEQ ID NO:93:</li><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 45 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>	
50	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:	
55	GGATGGGGAT CCTCACAAGA CAAGGCAACC AGATTTTTC TTCCC	45

	(2) INFORMATION FOR SEQ ID NO:94:		
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 29 base pairs		
5	(B) TYPE: nucleic acid		
	<pre>(C) STRANDEDNESS: single (D) TOPOLOGY: linear</pre>		
٠	(b) Topobogi: Timear		
		•	
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:	•	•
	GGGAAGCTTC CATGAGCGAG ACGGTCATC		29
15	(2) INFORMATION FOR SEQ ID NO:95:		
	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 28 base pairs		
	(B) TYPE: nucleic acid		
20	<pre>(C) STRANDEDNESS: single (D) TOPOLOGY: linear</pre>		
20	(D) TOPOLOGY: Timear		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:		
25	CCCGGATCCT CAGGGAGAAC CCCGCTTC		28
	(2) INFORMATION FOR SEQ ID NO:96:		
	(i) SEQUENCE CHARACTERISTICS:		
30	(A) LENGTH: 30 base pairs		
	(B) TYPE: nucleic acid		
	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	,	
	(2)		
35			
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:		
	GTGAATTCGA CCATGGAGCG GCCCCCGGGG		30
40	(2) INFORMATION FOR SEQ ID NO:97:		
	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 27 base pairs		
	(B) TYPE: nucleic acid		
45	(C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:		
50	amagna ang magnaman na an ang		27
	GTGGTACCCA TTCTGTTAAC CAACTCC		4,1
	(2) INFORMATION FOR SEQ ID NO:98:		
55	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 28 base pairs		
			189

	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
_		
5	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:	
	(XI) SEQUENCE DESCRIPTION: SEQ ID NO. 96:	
	GTGGTACCTC ATTCTGTTAA CCAACTCC	28
10	(2) INFORMATION FOR SEQ ID NO:99:	•
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 28 base pairs	,
٠	(B) TYPE: nucleic acid	
15	(C) STRANDEDNESS: single	*
	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:	
20	(AI) DEGOLACE DEBONITION. DEG ID NO. 33.	
	GTCTCGAGAG ATGCTGTCCC GTGGGTGG	28
	(2) INFORMATION FOR SEQ ID NO:100:	
		• .
25	(i) SEQUENCE CHARACTERISTICS:	•
	(A) LENGTH: 27 base pairs	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
30	(D) TOPOBOGI: TIMEAT	
00	•	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:	
	GTGAATTCGC TTCCTCTTGA GGGAACC	27
35		
	(2) INFORMATION FOR SEQ ID NO:101:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 27 base pairs	
40	(B) TYPE: nucleic acid	
70	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
	·	
45	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:	
	GTGAATTCAC TTCCTCTTGA GGGAACC	27
	(a) THEODWANTON FOR CEO TO NO. 102.	
50	(2) INFORMATION FOR SEQ ID NO:102:	·
30	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 29 base pairs	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
55	(D) TOPOLOGY: linear	

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:	·
_	GTCTCGAGCC ATGGAGAACT TCCAAAAGG	29
5	(2) INFORMATION FOR SEQ ID NO:103:	
	(i) SEQUENCE CHARACTERISTICS:	
40	(A) LENGTH: 28 base pairs (B) TYPE: nucleic acid	
10	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
15	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:	
	GTGGATCCCA GAGTCGAAGA TGGGGTAC	28
	(2) INFORMATION FOR SEQ ID NO:104:	
20	(1)	
	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 29 base pairs</li></ul>	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
25	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:	
30	GTGGATCCTC AGAGTCGAAG ATGGGGTAC	29
	(2) INFORMATION FOR SEQ ID NO:105:	
	(i) SEQUENCE CHARACTERISTICS:	
35	(A) LENGTH: 30 base pairs	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
40		
40	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:	•
	GTGAATTCGG CGATGCCAGA CCCCGCGGCG	30
45	(2) INFORMATION FOR SEQ ID NO:106:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 32 base pairs	
	(B) TYPE: nucleic acid	
50	<ul><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:	
55	(XI) SEGORNCE PERCEISITON: SEG ID NO:100:	
	GTGGATCCCA GGCACAGGCA GCCTCAGCCT TC	32
		191

			(2)	INF	'ORMA	TION	FOR	SEQ	ID	NO:1	07:					•		
5		(i	(A) (B) (C)	LENG TYPE STRA	TH: : nu NDED	33 b clei NESS	CTER ase c ac : si near	pair id ngle	S									
10		. (x	ci) S	EQUE	NCE	DESC	RIPT	'ION :	SEÇ	) ID	NO:1	07:						
	GTGG	ATC	CTC P	.GGCA	CAGG	C AC	CCTC	AGCC	TTC	2							33	
15			(2)	INF	ORMA	MOIT	FOR	SEC	) ID	NO:1	08:							
20		<b>(</b> )	(A) (B) (C)	LENG TYPE STRA	TH: : nu NDEL	2616 clei NESS	CTER bas c ac s: si near	e pa id ngle	irs									
25			(x) (A)	EATU NAN	JRE: ME/KI	EY: C	e: cE	ıg Se	equer	nce							•	
			(D)	OTI	IER I	NFOF	LTAMS	ON:										
30		()	ci) S	EQUE	ENCE	DESC	RIPT	ION:	SEÇ	Q ID	NO:1	.08:						
							GAG Glu										48	
35							GTA Val										96	÷
40							ACC										144	
45							CCC Pro 55										192	
50							TGC Cys										240	
55							TCC Ser										288	
55	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	GCC	GAG	336	192

																	*
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu	•
5				GAG Glu													384
10				AAG Lys													432
				AGC Ser										_			480
15				GTG Val													528
20	-,			GCC Ala 180													576
25				CTG Leu											_		624
30				CCC Pro												TTC . Phe	672
05				GCC Ala													720
35				TCT Ser													768
40				CTG Leu 260													816
45				CTG Leu													864
50				CTG Leu			-										912
				TTC Phe													960
55	TAC	GCC	ATT	GCC	GGC	GGC	AAA	GCG	CAC	TGT	GGA	CCG	GCA	GAG	CTC	TGC	1008

	Tyr	Ala	Ile	Ala	Gly 325	Gly	Lys	Ala	His	Cys 330	Gly	Pro	Ala	Glu	Leu 335	Суѕ	
5					CGC												1056
10					CCG Pro												1104
15					GCC Ala											AAG Lys	1152
10					GCC Ala												1200
20					ATT Ile 405												1248
25					ACG Thr												1296
30					GGC Gly												1344
25					TCC Ser												1392
35					AAG Lys												1440
40					TGG Trp 485												1488
45					TGC Cys								Ser				1536
50					GCT Ala				Thr								1584
					CAG Gln	Arg											1632
55	ACC	CCT	GAG	CCA	GCA	CGC	ATA	ACG	TCC	CCA	GAC	AAA	CCG	CGG	CCG	ATG	1680

										100							
	Thr 545	Pro	Glu	Pro	Ala	Arg 550	Ile	Thr	Ser	Pro	Asp 555	Lys	Pro	Arg	Pro	<b>Met</b> 560	
5		ATG Met															1728
10		AAG Lys															1776
		ATT Ile							•								1824
15		CGC Arg 610									Ala					AAG Lys	1872
20		GGC Gly															1920
25		ATG Met															1968
30		CAG Gln															2016
		CTG Leu															2064
35		GTG Val 690				Leu		Gln								CTG Leu	2112
40																CTG Leu 720	2160
45		GTT Val														AAA Lys	2208
50																AAG Lys	2256
. ۔ دع									Glu							TTC Phe	2304
55	TCC	AGC	CGC	AGC	GAT	GTC	TGG	AGC	TAT	GGG	GTC	ACC	ATG	TGG	GAG	GCC	2352

	Ser	Ser 770	Arg	Ser	Asp		Trp 775	Ser	Tyr	Gly	Val	Thr 780	Met	Trp	Glu	Ala	
5		TCC Ser															2400
10		GCC Ala		Ile													2448
		CCC Pro														TGG Trp	2496
15		GAT Asp															2544
20		TAC Tyr 850														CAG Gln	2592
25		GCT Ala						TGA									2616
30		. (:	i) SI (A) (B)	EQUEI LENG TYPI	NCE ( STH: E: a:	ATION CHARA 871 mino	ACTEI amii acio	RIST: no a	ICS: cids	NO:	109:						
35		(:	(D)	TOP	OLOG.	DNES: Y: 1: TYP:	inea	r									
40		(¬	v) FI	RAGM	ENT '	TYPE DES	: in	tern	al	Q ID	NO:	109:					
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	
45				20					25					30		Gly	
			35					40					45			Ile Thr	·
50	_	50		_			55					60				Lys 80	
					85					90					95	Glu	
55				100					105	į.				110	)	Glu Gly	
		•	_		-	-					_				-	_	40

			115					120					125			
	Ile	Asp 130		Lys	Glu	Asp	Gly 135	Asn	Ile	Leu	Gly	His 140	Lys	Leu	Glu	Tyr
5	Asn 145	Tyr	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	Asp	Lys	Gln	Lys	Asn 160
	Gly	Ile	Lys	Val	Asn 165	Phe	Lys	Ile	Arg	His 170	Asn	Ile	Glu	Asp	Gly 175	
	Val	Gln	Leu	Ala 180	qaA	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly
10			195			_		200	_				205		Ala	
		210	_				215					220			Glu	
15	225				_	230					235				Lys	240
	-				245					250					Asp 255	
				260					265					270	Glu	
20	•		275					280					285		Leu	
	_	290	-				295		_	_		300			Val	
25	305		_			310					315				Gly Leu	320
	-				325					330					335 Arg	
30		·	_	340					345					350	Phe	
30		-	355					360					365		Trp	
	-	370					375					380				Gln
35	385		_			390					395					400 Tyr
					405					410					415	Gly
40				420					425					430		Gly
			435					440					445			Leu
		450					455					460				Lys
45	465					470					475					480 Asp
		_			485					490					495	
50	=			500					505					510		Thr
			515					520					525			Tyr
		530					535					540				Met
55	545 Pro	Met	Asp	Thr	Ser	550 Val		Glu	Ser	Pro	555 Tyr		Asp	Pro	Glu	560 Glu

```
570
     Leu Lys Asp Lys Lys Leu Phe Leu Lys Arg Asp Asn Leu Leu Ile Ala
                                      585
     Asp Ile Glu Leu Gly Cys Gly Asn Phe Gly Ser Val Arg Gln Gly Val
5
     Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile Lys Val Leu Lys
                             615
     Gln Gly Thr Glu Lys Ala Asp Thr Glu Glu Met Met Arg Glu Ala Gln
                          630
                                              635
10
     Ile Met His Gln Leu Asp Asn Pro Tyr Ile Val Arg Leu Ile Gly Val
                      645
                                          650
     Cys Gln Ala Glu Ala Leu Met Leu Val Met Glu Met Ala Gly Gly Gly
                                      665
     Pro Leu His Lys Phe Leu Val Gly Lys Arg Glu Glu Ile Pro Val Ser
                                 680
15
      Asn Val Ala Glu Leu Leu His Gln Val Ser Met Gly Met Lys Tyr Leu
                              695
      Glu Glu Lys Asn Phe Val His Arg Asp Leu Ala Ala Arg Asn Val Leu
                          710
                                              715
      Leu Val Asn Arg His Tyr Ala Lys Ile Ser Asp Phe Gly Leu Ser Lys
20
                      725
                                          730
      Ala Leu Gly Ala Asp Asp Ser Tyr Tyr Thr Ala Arg Ser Ala Gly Lys
                                      745
      Trp Pro Leu Lys Trp Tyr Ala Pro Glu Cys Ile Asn Phe Arg Lys Phe
25
                                  760
      Ser Ser Arg Ser Asp Val Trp Ser Tyr Gly Val Thr Met Trp Glu Ala
                              775
      Leu Ser Tyr Gly Gln Lys Pro Tyr Lys Lys Met Lys Gly Pro Glu Val
                          790
                                              795
      Met Ala Phe Ile Glu Gln Gly Lys Arg Met Glu Cys Pro Pro Glu Cys
30
                                          810
      Pro Pro Glu Leu Tyr Ala Leu Met Ser Asp Cys Trp Ile Tyr Lys Trp
                                      825
      Glu Asp Arg Pro Asp Phe Leu Thr Val Glu Gln Arg Met Arg Ala Cys
35
                                  840
      Tyr Tyr Ser Leu Ala Ser Lys Val Glu Gly Pro Pro Gly Ser Thr Gln
      Lys Ala Glu Ala Ala Cys Ala
                          870
40
               (2) INFORMATION FOR SEQ ID NO:110:
            (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 2598 base pairs
45
              (B) TYPE: nucleic acid
              (C) STRANDEDNESS: single
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: cDNA
50
            (ix) FEATURE:
               (A) NAME/KEY: Coding Sequence
               (B) LOCATION: 1...2595
               (D) OTHER INFORMATION:
55
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:
```

																	•
	Met													AGC Ser			48
_	1				5					10					10		
5				~~~	~~~	~~~	~~~	ama		ama.	000	000	3 mc	000	CAC	ccc	96
														GCG			. 30
	Arg	Ala	GIU		GIU	GIU	HIS	Leu		Leu	Ala	GIY	Met	Ala 30	App	GIY	
				20					25					30			
10	CmC	ጥጥር	CTC:	CTC	CGC	CAG	TGC	CTG	CGC	TCG	СТС	GGC	GGC	TAT	GTG	CTG	144
. 10														Tyr			
	, neu	FIIC	35	200	- T- 9	01	<b>-</b> 75	40	•••=			<b>-</b> -7	45	-1-			
	TCG	CTC	GTG	CAC	GAT	GTG	CGC	TTC	CAC	CAC	TTT	CCC	ATC	GAG	CGC	CAG	192
15														Glu			
		50			_		55				•	60					
				•													
														TGT			240
	Leu	Asn	Gly	Thr	Tyr	Ala	Ile	Ala	Gly	Gly	Lys	Ala	His	Cys	Gly	Pro.	
20	65					70					75					80	
												~~~	~~~	amia	000	maa	200
														CTG			288
	Ala	GIU	Leu	Cys		Pne	Tyr	ser	Arg		Pro	Asp	GIY	Leu	95	Cys	
25					85					90					95		
25	220	CTC	cac	אאכ	CCG	тсс	מממ	caa	CCG	тсс	GGC	רידיר	GAG	CCG	CAG	CCG	336
														Pro			550
	NO.	LCu.	••••	100		0,0	••••	• 5	105		4 -7			110			
30	GGG	GTC	TTC	GAC	TGC	CTG	CGA	GAC	GCC	ATG	GTG	CGT	GAC	TAC	GTG	CGC	384
														Tyr			
	=		115					120					125				
-																	
														ATC			432
35	Gln		Trp	Lys	Leu	Glu	Gly	Glu	Ala	Leu	Glu		Ala	Ile	Ile	Ser	
		130					135					140					
					ama	~~~				a.a.m		200	000	an a	CAC	ccc	480
														CAC			400
40		Ala	PIO	GIII	vai	150	гуя	Leu	116	Ald	155	TIII	ATG	His	Giu	160	
40	145					130	:				133					100	
	ATG	CCC	TGG	TAC	CAC	AGC	AGC	CTG	ACG	CGT	GAG	GAG	GCC	GAG	CGC	AAA	528
														Glu			
				- 2 -	165		•			170					175		
45																	
	CTT	TAC	TCT	GGG	GCG	CAG	ACC	GAC	GGC	AAG	TTC	CTG	CTG	AGG	CCG	CGG	576
	Leu	Tyr	Ser	Gly	Ala	Gln	Thr	Asp	Gly	Lys	Phe	Leu	Leu	Arg	Pro	Arg	
				180					185					190		•	
50																GTG	624
	Lys	Glu		Gly	Thr	Tyr	Ala			Leu	Ile	Tyr			Thr	Val	
			195					200					205				
			- -		3.55	» ~ ~	03 -	a > ~					m» ~) Ame		672
EE																CCC	672
55	Tyr		ıyr	ьeu	TTE	ser		_	ьys	WIS	стА			cys	TTE	Pro	
		210					215					220					

5		GGC Gly															720
		AAG Lys															768
10	Ser	AGT Ser	Ala	Ser 260	Asn	Ala	Ser	Gly	Ala 265	Ala	Ala	Pro	Thr	Leu 270	Pro	Ala	816
15	His	CCA Pro	Ser 275	Thr	Leu	Thr	His	Pro 280	Gln	Arg	Arg	Ile	Asp 285	Thr	Leu	Asn	864
20	Ser	GAT Asp 290	Gly	Tyr	Thr	Pro	Glu 295	Pro	Ala	Arg	Ile	Thr 300	Ser	Pro	Asp	Lys	912
25	Pro 305	CGG Arg	Pro	Met	Pro	Met 310	Asp	Thr	Ser	Val	Tyr 315	Glu	Ser	Pro	Tyr	Ser 320	960
		CCA Pro															1008
30		CTC Leu															1056
35	Arg	CAG Gln	Gly 355	Val	Tyr	Arg	Met	Arg 360	Lys	Lys	Gln	Ile	Asp 365	Val	Ala	Ile	1104
40	Lys	GTG Val 370	Leu	Lys	Gln	Gly	Thr 375	Glu	Lys	Ala	Asp	Thr 380	Glu	Glu	Met	Met	1152
45		GAG Glu															1200
		ATT Ile															1248
50		GGG Gly															1296
55		CCT Pro															1344

5		AAG Lys 450								1392
		AAC Asn								1440
10		CTC Leu								1488
15		GCA Ala				Tyr				1536
20		CGC Arg								1584
25		TGG Trp 530							AAA Lys	1632
		CCG Pro								1680
30		CCA Pro								1728
35		TAC Tyr								1776
40		CGA Arg								1824
45		AGC Ser 610								1872
		ACC Thr								1920
50	ATC Ile	CTG Leu								1968
55		GGC Gly								2016

		ATC Ile								_	2064
5		ACC Thr 690					Ser				2112
10		AAG Lys	•								2160
15		GAG Glu							_		2208
20		GAG Glu									2256
25		GGC Gly									2304
		TAC Tyr 770									2352
30		AAC Asn									2400
35		AGC Ser									2448
40		GGC Gly									2496
45		CTG Leu									2544
		TTC Phe 850			Ile			Asp			2592
50	AAG Lys 865										2598

55 (2) INFORMATION FOR SEQ ID NO:111:

203

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 865 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5

55

- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal
- 10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

Met Pro Asp Pro Ala Ala His Leu Pro Phe Phe Tyr Gly Ser Ile Ser Arg Ala Glu Ala Glu Glu His Leu Lys Leu Ala Gly Met Ala Asp Gly 15 Leu Phe Leu Leu Arg Gln Cys Leu Arg Ser Leu Gly Gly Tyr Val Leu Ser Leu Val His Asp Val Arg Phe His His Phe Pro Ile Glu Arg Gln 20 Leu Asn Gly Thr Tyr Ala Ile Ala Gly Gly Lys Ala His Cys Gly Pro 70 75 Ala Glu Leu Cys Glu Phe Tyr Ser Arg Asp Pro Asp Gly Leu Pro Cys Asn Leu Arg Lys Pro Cys Asn Arg Pro Ser Gly Leu Glu Pro Gln Pro 25 Gly Val Phe Asp Cys Leu Arg Asp Ala Met Val Arg Asp Tyr Val Arg 120 Gln Thr Trp Lys Leu Glu Gly Glu Ala Leu Glu Gln Ala Ile Ile Ser 135 140 30 Gln Ala Pro Gln Val Glu Lys Leu Ile Ala Thr Thr Ala His Glu Arg 150 155 Met Pro Trp Tyr His Ser Ser Leu Thr Arg Glu Glu Ala Glu Arg Lys 170 Leu Tyr Ser Gly Ala Gln Thr Asp Gly Lys Phe Leu Leu Arg Pro Arg 35 185 Lys Glu Gln Gly Thr Tyr Ala Leu Ser Leu Ile Tyr Gly Lys Thr Val 200 Tyr His Tyr Leu Ile Ser Gln Asp Lys Ala Gly Lys Tyr Cys Ile Pro 215 220 40 Glu Gly Thr Lys Phe Asp Thr Leu Trp Gln Leu Val Glu Tyr Leu Lys 230 235 Leu Lys Ala Asp Gly Leu Ile Tyr Cys Leu Lys Glu Ala Cys Pro Asn 245 250 Ser Ser Ala Ser Asn Ala Ser Gly Ala Ala Pro Thr Leu Pro Ala 45 His Pro Ser Thr Leu Thr His Pro Gln Arg Arg Ile Asp Thr Leu Asn 280 Ser Asp Gly Tyr Thr Pro Glu Pro Ala Arg Ile Thr Ser Pro Asp Lys 295 300 50 Pro Arg Pro Met Pro Met Asp Thr Ser Val Tyr Glu Ser Pro Tyr Ser 310

Asp Pro Glu Glu Leu Lys Asp Lys Leu Phe Leu Lys Arg Asp Asn

Leu Leu Ile Ala Asp Ile Glu Leu Gly Cys Gly Asn Phe Gly Ser Val

Arg Gln Gly Val Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile

330

			355					360					365			
	Lvs	Val		Lys	Gln	Gly	Thr		Lys	Ala	Asp			Glu	Met	Met
	-1-	370		•		•	375		•		_	380				
	Arg	Glu	Ala	${\tt Gln}$	Ile	Met	His	Gln	Leu	Asp	Asn	Pro	Tyr	Ile	Val	Arg
5	385					390					395					400
	Leu	Ile	Gly	Val	_	Gln	Ala	Glu	Ala		Met	Leu	Val	Met		Met
		~ 3		-	405	·	•••		D 1	410	7	01	.		415	~ 1
	Ата	GIY	GIY	420	PIO	теп	HIS	гаг	425	ьeu	vaı.	GIY.	гув	Arg	GIU	GIU
10	Tle	Pro	Val		Asn	Val	Ala	Glu		Leu	His	Gln	Val	Ser	Met	Glv
			435					440					445			
	Met	Lys	Tyr	Leu	Glu	Glu	Lys	Asn	Phe	Val	His	Arg	Asp	Leu	Ala	Ala
		450					455					460				_
	_		Val	Leu	Leu		Asn	Arg	His	Tyr		Lys	Ile	Ser	Asp	
15	465		Sor.	Tura	- ו ת	470	C111	λl-	7 ~~	7 ~~	475	The same	TT	Thr	λls	480
	GIY	Den	PET	цуъ	485	теп	GIA	WIG	Asp	490	ser	TÀT	ıyı	1111	495	Arg
	Ser	Ala	Gly	Lys		Pro	Leu	Lys	Trp		Ala	Pro	Glu	Cys		Asn
			-	500	-			. •	505	•				510	•	
20	Phe	Arg	Lys	Phe	Ser	Ser	Arg	Ser	Asp	Val	Trp	Ser	Tyr	Gly	Val	Thr
			515		_	_	_	520		_	_	_	525	_		_
	Met	_	Glu	Ala	Leu	Ser	Tyr 535	GIY	Gln	Lys	Pro	Tyr 540	Lys	Lys	Met	rys
	Glv	530 Pro	Glu	Val	Met	Δla		Tle	Glu	Gln	Glv		Δra	Met	Glu	Cvs
25	545	FLO	oru			550	1110	110	014	0111	555	Lys	9			560
		Pro	Glu	Cys	Pro	Pro	Glu	Leu	Tyr	Ala	Leu	Met	Ser	Asp	Cys	Trp
				_	565				_	570					575	
	Ile	Tyr	Lys		Glu	Asp	Arg	Pro	_	Phe	Leu	Thr	Val	Glu	Gln	Arg
00				580				•	585		•	**- 3	a1	590	Ď	D
30	Met	Arg	A1a 595	Cys	Tyr	Tyr	ser	600	Ата	ser	гув	vaı	605	Gly	PIO	PIO
	Glv	Ser		Gln	Lvs	Ala	Glu		Ala	Cvs	Ala	Trp		Pro	Pro	Val
	027	610					615			-7-		620				
	Ala	Thr	Met	Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro
35	625					630					635					640
	Ile	Leu	Val	Glu		Asp	Gly	Asp	Val		Gly	His	ГÀв	Phe		Val
	Com	~1··	Gl 11	Clv	645	Clv	y an	- ומ	The	650	G] v	Lare	T.611	Thr	655	Lve
	ser	GIY	GIU	660	Gru	Gry	Asp	MIG	665	ıyı	GIY	пуъ	пец	670	Deu	LJ S
40	Phe	Ile	Cys		Thr	Gly	Lys	Leu		Val	Pro	Trp	Pro	Thr	Leu	Val
			675			_	_	680			•	_	685			
	Thr	Thr	Leu	Thr	Tyr	Gly		Gln	Cys	Phe	Ser		Tyr	Pro	Asp	His
		690			_	_,	695	_	_			700		~ 7		**- 7
45		ГÀв	Gin	Hls	Asp	710	Pne	гуs	ser	Ата	Met 715	Pro	GIU	Gly	Tyr	720
40	705 Gln	Glu	Ara	Thr	Ile		Phe	Lvs	Asp	Asp		Asn	Tvr	Lys	Thr	
	01	01	5		725			-1-		730	4-1		-1-	-1-	735	5
	Ala	Glu	Val	Lys	Phe	Glu	Gly	Asp	Thr	Leu	Val	Asn	Arg	Ile	Glu	Leu
				740					745					750		
50	Lys	Gly		Asp	Phe	Lys	Glu		Gly	Asn	Ile	Leu		His	Lys	Leu
		~	755		7	0	***	760	••- 1		-1 -	\/ - L	765		T	
	GIU	777	ASII	Tyr	ASN	ser	775	ASN	val	ryr	тте	мес 780	мта	Asp	пĀг	GIN
	Lvs		Glv	Ile	Lvs	Val		Phe	Lvs	Ile	Ara		Asn	Ile	Glu	Asp
55	785		- 4		•	790					795					800
	Gly	Ser	Val	Gln	Leu	Ala	Asp	His	Tyr	Gln	Gln	Asn	Thr	Pro	Ile	Gly

										205								
					805					810					815		•	
	Asp	Gly	Pro	Val 820	Leu	Leu	Pro	Asp	Asn 825	His	Tyr	Leu	Ser	Thr 830	Gln	Ser		
5	Ala	Leu	Ser 835	Lys	Asp	Pro	Asn	Glu 840	Lys	Arg	Asp	His	Met 845	Val	Leu	Leu		
	Glu	Phe 850		Thr	Ala	Ala	Gly 855		Thr	Leu	Gly	Met 860		Glu	Leu	Tyr		
٠	Lys	850					655					860						•
10	865																	
	:		(2)	INF	ORMA	TION	I FOR	SEÇ) ID	NO:	.12:							
15		i)	(A) (B) (C)	EQUEN LENG TYPE STRA	TH: : nu ANDEL	1635 Iclei NESS	bas c ac : si	se pa cid ingle	airs									
20				OLEC FEATU		TYPE	E: CI	AAC		,								
25			(B)	NAM LOC OTI	CATIO	ON: I	L1	1632	equei	nce								
		. (3	ki) S	SEQUE	ENCE	DESC	CRIPT	rion	: SE	Q ID	NO:	112:						
30				TTC Phe												Gly	48	
05				AAA Lys 20													.96	
35			Ile	CGC Arg	Leu	Asp	Thr	Glu	Thr		Gly	Val	Pro				144	
40				ATC Ile													192	
45				GAT Asp													240	
50				CAC His													288	
55				CCT Pro 100						Ser					Leu		336	
JÜ	CAG	GGC	CTA	GCT	TTC	TGC	CAT	TCT	CAT	CGG	GTC	CTC	CAC	CGA	GAC	CTT	384	205

	Gln	Gly	Leu 115	Ala	Phe	Cys	His	Ser 120	His	Arg	Val	Leu	His 125	Arg	Asp	Leu		
5		CCT Pro 130															432	
10		TTT Phe															480	
15		GAG Glu														GGC Gly	528	-
		AAA Lys															576	
20		GCT Ala															624	
25		GAC Asp 210															672	
30		GTG Val															720	
0.5		AAG Lys															768	
35		GAT Asp														AAC Asn	816	
40		CGG Arg															864	
4 5		ACC Thr 290															912	
50		ATG Met															960	•
		GTC Val															1008	
55	GGC	GAG	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	AAG	CTG	ACC	CTG	AAG	TTC	1056	206

207

									•	201								
	Gly	Glu	Gly	Glu 340	Gly	Asp	Ala	Thr	Tyr 345	Gly	Lys	Leu	Thr	Leu 350	Lys	Phe		٠
	איניכ	TCC	ארכ	ACC	GGC	D D G	CTG	כככ	стс	ccc	тсс	CCC	אככ	כיזיכי	CTC	ACC		1104
5												Pro						1104
	116	Cys	355	1111	Cly	ביים	Deu	360	Vai	710	· · ·	110	365	Deu	V 41			
•	ACC	CTG	ACC	TAC	GGC	GTG	CAG	TGC	TTC	AGC	CGC	TAC	CCC	GAC	CAC	ATG		1152
	Thr	Leu	Thr	Tyr	Gly	Val	Gln	Cys	Phe	Ser	Arg	Tyr	Pro	Asp	His	Met		
10		370					375					380						
	AAG	CAG	CAC	GAC	TTC	TTC	AAG	TCC	GCC	ATG	ccc	GAA	GGC	TAC	GTC	CAG		1200
												Glu						*
	385					390					395					400		
15																		
												TAC						1248
	Glu	Arg	Thr	Ile		Phe	Lys	Asp	qaA	_	Asn	Tyr	Lys	Thr	_	Ala		
					405					410					415			
20	GAG	GTG	AAG	TTC	GAG	GGC	GAC	ACC	CTG	GTG	AAC	CGC	ATC	GAG	CTG	AAG		1296
	Glu	Val	Lys	Phe	Glu	Gly	Asp	Thr	Leu	Val	Asn	Arg	Ile	Glu	Leu	Lys		
				420					425					430				
	000	n micr	a.a	mma	220	a. a	a. a	999		N M G	ama	999	G 2 G		ama			1344
25												GGG Gly						1344
25	Gry	110	435	FIIC	пув	GIU	veħ	440	ASII	116	Dea	GIY	445	цуз	Deu	GIU		
	TAC	AAC	TAC	AAC	AGC	CAC	AAC	GTC	TAT	ATC	ATG	GCC	GAC	AAG	CAG	AAG		1392
	Tyr	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	Ala	Asp	Lys	Gln	Lys		
30		450					455					460						
	מממ	GGC	ATC	AAG	GTG	AAC	TTC	AAG	ATC	CGC	CAC	AAC	ATC	GAG	GAC	GGC		1440
												Asn				_		
	465	-				470		•		_	475				_	480		
35																		
												ACC						1488
	Ser	Val	Gln	Leu		_	His	Tyr	Gln		Asn	Thr	Pro	Ile		Asp		
					485					490					495			
40	GGC	CCC	GTG	CTG	CTG	ccc	GAC	AAC	CAC	TAC	CTG	AGC	ACC	CAG	TCC	GCC		1536
												Ser						
	_			500			_		505	-				510				
45												ATG						1584
45	Leu	Ser		Asp	Pro	Asn	GIU	_	Arg	Asp	Hls	Met		ren	Leu	GIU		
			515					520					525					
	TTC	GTG	ACC	GCC	GCC	GGG	ATC	ACT	CTC	GGC	ATG	GAC	GAG	CTG	TAC	AAG	Т	1633
												Asp						
50		530				_	535					540			_	•		
	AA																	1635

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:

55

(A) LENGTH: 544 amino acids(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: protein
 (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

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10		_				_			_					_,		
	Met	Glu	Asn	Phe	Gln	Lys	Val	Glu	Lys	Ile	GIY	GIu	GIA	Thr		GIY
	1				5					10					15	
	Val	Val	Tyr	Lys	Ala	Arg	Asn	Lys	Leu	Thr	Gly	Glu	Val	Val	Ala	Leu
			•	20		-		-	25					30		
15	Tare	LVC	Tle	Ara	Len	Δεη	Thr	Glu	Thr	Glu	Glv	Val	Pro	Ser	Thr	Ala
10	пув	Lly U	35	**** 9	LCu	,,op		40		0_0	- 1		45			
		-			_	_	_		~~		~	***		3	T1 -	17-1
	Ile	Arg	GIu	11e	Ser	Leu		ьуs	GIU	Leu	Așn		Pro	Asn	тте	vai
		50					55					60			_	
	Lys	Leu	Leu	Asp	Val	Ile	His	Thr	Glu	Asn	Lys	Leu	Tyr	Leu	Val	Phe
20	65					70					75					80
	Glu	Phe	Leu	His	Gln	qaA	Leu	Lys	Lys	Phe	Met	Asp	Ala	Ser	Ala	Leu
					85	•		•	-	90		_			95	
	Thr	Glv	Tle	Pro		Pro	T.em	Tle	LVS	Ser	ጥህዮ	Len	Phe	Gln	Leu	Leu
	1111	GIY	110	100	Deu	110	LCu		105	501	-1-			110		
05		-3	•		D1	~	*** -	~		3	17-3	¥	775.0		7 ~~	Ton
25	Gin	GIA		АТА	Pne	Cys	HIS		HIS	Arg	vai	neu		Arg	Asp	ьеu
			115					120					125		_	
	Lys	Pro	Gln	Asn	Leu	Leu	·Ile	Asn	Thr	Glu	Gly	Ala	Ile	Lys	Leu	Ala
		130					135					140				
	Asp	Phe	Gly	Leu	Ala	Arg	Ala	Phe	Gly	Val	Pro	Val	Arg	Thr	Tyr	Thr
30	145					150	•				155					160
	His	Glu	Val	Val	Thr	Leu	Trp	Tyr	Arq	Ala	Pro	Glu	Ile	Leu	Leu	Gly
					165				5	170					175	_
	Co~	Lve	ጥላታም	ጥረታ		Thr	7.1 =	V=1	Acn		Trn	Ser	Len	Gly		Ile
	261	цуб	ıyı		561	1111	AIG	VAI		110	111			190	O _I J	
				180		_,	_	_	185		D1	D	a 1		C	a 1
35	Phe	Ala		Met	val	Thr	Arg		Ата	Leu	Pne	PIO		Asp	Set	GIU
			195					200				_	205			
	Ile	Asp	Gln	Leu	Phe	Arg	Ile	Phe	Arg	Thr	Leu		Thr	Pro	Asp	GIu
		210					215					220				
	Val	Val	Trp	Pro	Gly	Val	Thr	Ser	Met	Pro	Asp	Tyr	Lys	Pro	Ser	Phe
40	225					230					235					240
		Lvs	Tro	Ala	Ara	Gln	Asp	Phe	Ser	Lvs	Val	Val	Pro	Pro	Leu	Asp
		-,-			245					250					255	-
•	63.	7 02	Gly	7~~		T.011	Len	Co.	Gln		T.A11	Wie	ጥህን	Asp		Asn
	GIU	Asp	Gry		SET	пец	neu	Ser		Met	Dea	111.5	- 7 -	270	110	
4-	_	_		260		_			265			D	mh -	_	61 m	7
45	Lys	Arg		Ser	Ala	гÀг	Ala			Ala	HIS	Pro			GIII	Asp
			275					280					285		_	
	Val	Thr	Lys	Pro	Val	Pro	His	Leu	Arg	Ļeu	Trp	Asp	Pro	Pro	Val	Ala
		290					295					300				
	Thr	Met	Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile
50	305				_	310					315					320
			Glu	Leu	asp	Glv	Asn	Val	Asn	Glv			Phe	Ser	Val	Ser
	200				325	1				330					335	
	~ 1	~ 1	C1	G1		λ ~~	7 l ~	mb	т			1.011	ጥh ~	1.011		Phe
	GTĀ	GIU	GIY		Gry	wab	мта	THE			пåв	πeα	* 117			
		_		340	~~	_	_	_	345		_	n	m1-	350		mh
55	Ile	Cys		Thr	GTĀ	гÀг	Leu			Pro	Trp	Pro			val	Thr
			355					360					365			

	Thr	Leu 370	Thr	Tyr	Gly	Val	Gln 375	Cys	Phe	Ser	Arg	Tyr 380	Pro	Asp	His	Met	•
	Lys 385	Gln	His	Asp	Phe	Phe 390	Lys	Ser	Ala	Met	Pro 395	Glu	Gly	Tyr	Val	Gln 400	
5		Arq	Thr	Ile	Phe		Lys	Asp	Asp	Gly		Tyr	Lys	Thr	Arq		
					405	•	•	•	. •	410		.*	•		415		
	Glu	Val	Lys		Glu	Gly	Asp	Thr		Val	Asn	Arg	Ile		Leu	Lys	
	01	-7-	7	420	T	01	n	a 1	425	- 1 -	.	01	77.2 m	430	T	~ 1	
10	GIA	TTE	435	Pne	Lys	GIU	Asp	G1Y	Asn	TTE	ьеп	GIY	H1S	гÀг	Leu	GIU	
10	Tyr	Asn 450		Asn	Ser	His	Asn 455		Tyr	Ile	Met	Ala 460		Lys	Gln	Lys	
	Asn	Gly	Ile	Lys	Val	Asn	Phe	Lys	Ile	Arg	His	Asņ	Ile	Glu	Asp	Gly	
	465					470					475					480	
15	Ser	Val	Gln	Leu	Ala 485		His	Tyr	Gļn	Gln 490	Asn	Thr	Pro	Ile	Gly 495	Asp	
	Gly	Pro	Val		Leu	Pro	Asp	Asn		Tyr	Leu	Ser	Thr		Ser	Ala	
	Tou	Cor	Lvc	500	Pro	N G D	Glu	Tare	505	y an	иia	Mot	บาโ	510	Len	Gl 11	
20	neu	261	515	veb	·	ASII	GIU	520	Arg	web	uTP	MEC	525	men	neu	GIU	
	Phe	Val		Ala	Ala	Gly	Ile		Leu	Gly	Met	Asp		Leu	Tyr	Lys	
	•	530					535			_		540			-	-	
			(0)	T 271	ao D.W.	MTO	. 501			***							
25			(2)) INI	FORM	ÁLTOI	N FOI	K SE(מד נ	NO:.	114:						
20		(:	i) SI	EQUEI	VCE (CHAR	ACTE	RIST	ICS:								
			(A)	LEN	GTH:	163	bas	se pa	airs								
					E: ni												
30					ANDEI				9								
30			(D)	TOP	JUG.	I. 1.	inea	<u> </u>									
				MOLE FEAT	CULE URE:	TYPI	E: CI	ANC									
					4												
35					ME/KI CATIO			_	eque	nce							
					HER :												
													•				
		(2	xi) S	SEQUI	ENCE	DES	CRIP:	rion	: SE	QI Q	NO:	114:		•			
40		ama			000	G N G	a. a	ama	m ma		000	ama	ama	000	N.M.C	ama	
					GGC Gly												48
	1	val	261	Буз	5	Gra	Giu	пец	PILE	10	GIY	vai	Val	FIO	15	Deu	
					_												
45	GTC	GAG	CTG	GAC	GGC	GAC	GTA	AAC	GGC	CAC	AAG	TTC	AGC	GTG	TCC	GGC	96
	Val	Glu	Leu	_	Gly	Asp	Val	Asn	_	His	Lys	Phe	Ser		Ser	Gly	
				20					25					30			
	GAG	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	AAG	СТС	ACC	СТС	AAG	TTC	ATC	144
50					Asp												
		•	35	-	-			40	•	•			45	-			
												_					
					AAG											_	192
55	Cys	TDT	TIII	GTÅ	Lys	neu	Pro 55	val	PIO	TIP	PTO	TOT	ьeи	val	THE	TIIL	

		GGC Gly							240
5		TTC Phe							288
10		TTC Phe 100							336
15		GAG Glu						GGC Gly	384
		AAG Lys		Asn					432
20		AGC Ser							480
25		GTG Val							528
30		GCC Ala 180							576
35		CTG Leu							624
		CCC Pro							672
40		GCC Ala							720
45		TCT Ser							768
50		ACG Thr 260							816
55		GTG Val							864

		AGT Ser							912
5		AAT Asn							960
10		CTG Leu							1008
15		TCT Ser 340							1056
20		CAG Gln							1104
20		CGA Arg						GAG Glu	1152
25		AAG Lys							1200
30		ACT Thr							1248
35		CTC Leu 420							1296
40		GGC Gly							1344
40		GAT Asp							1392
45		CCA Pro							1440
50		CCA Pro							1488
55		CCC Pro 500							1536

									•	212								
								CGG Arg 520										1584
5								ACC Thr									Т	1633
	GA																	1635
10			(2)	INF	ORMA	OITA	I FOR	R SEC) ID	NO:1	.15:							
-		(i						RISTI									,	
15			(B) (C)	TYPE	: an	nino ONES	acio S: si	ingle										
20							_	rotei										
		()	(i) S	EQUI	ENCE	DES	CRIP	rion:	: SE	Q ID	NO:1	115:					•	
25	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile 15	Leu		
25		Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25		Lys	Phe	Ser	Val	Ser	Gly		
	Glu	Gly	Glu 35		Asp	Ala	Thr	Tyr 40		Lys	Leu	Thr	Leu 45	_	Phe	Ile		
30	Сув	Thr 50		Gly	Lys	Leu	Pro	Val	Pro	Trp	Pro	Thr		Val	Thr	Thr		
	Léu 65		Tyr	Gly	Val	Gln 70		Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys 80		
35		His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu		
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	naA	Tyr	Lys	Thr	Arg 110		Glu	L	
	Val	Lys	Phe 115	Glu	Gly	Asp	Thr	Leu 120	Val	Asn	Arg	Ile	Glu 125	Leu	Lys	Gly	•	
40	Ile	Asp 130	Phe	Lys	Glu	Asp	Gly 135	Asn	Ile	Leu	Gly	His 140		Leu	Glu	Tyr	•	
	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	Ala	Asp	Lys	Gln	Lys			
	145		_		_	150			_	•	155		~ 3	3	01.	160		
45	•		_		165			Ile		170					175			
				180				Gln	185					190				
			195					His 200					205					
50		210					215					220						
			Ala	Ala	GIÀ			Leu	Gly	Met			ьeи	ıyı	гу	Ser 240		
E E	225 Gly		Arg	Ser				Glu	Asn				Val	Glu	Lys 255	: Ile		
55	Gly	Glu	Gly	Thr	245 Tyr		Val	Val	Tyr	250 Lys		Arg	Asn	Lys			r	

				260					265					270			•
	Gly	Glu	Val 275	Val	Ala	Leu	Lys	Lys 280	Ile	Arg	Leu	Asp	Thr 285	Glu	Thr	Glu	
5	Gly	Val 290	Pro	Ser	Thr	Ala	Ile 295	Arg	Glu	Ile	Ser	Leu 300	Leu	Lys	Glu	Leu	
	Asn	His	Pro	Asn	Ile	Val	Lys	Leu	Leu	Asp	Val	Ile	His	Thr	Glu	Asn	
•	305					310					315				•	320	
	Lys	Leu	Tyr	Leu	Val 325	Phe	Glu	Phe	Leu	His 330	Gln	Asp	Leu	Lys	Lys 335	Phe	
10	Met	Asp	Ala	Ser 340	Ala	Leu	Thr	Gly	Ile 345	Pro	Leu	Pro	Leu	Ile 350	Lys	Ser	
	Tyr	Leu	Phe 355	Gln	Leu	Leu	Gln	Gly 360	Leu	Ala	Phe	Cys	His 365	Ser	His	Arg	
15	·Val	Leu 370	His	Arg	Asp	Leu	Lys 375	Pro	Gln	Asn	Leu	Leu 380		Asn	Thr	Glu	
	Gly 385	Ala	Ile	Lys	Leu	Ala 390		Phe	Gly	Leu	Ala 395		Ala	Phe	Gly	Val 400	
		Val	Arg	Thr	Tyr 405		His	Glu	Val	Val 410		Leu	Trp	туr	Arg 415		
20	Pro	Glu	Ile	Leu 420		Gly	Ser	Lys	Tyr 425		Sér	Thr	Ala	Val 430		Ile	
٠	Trp	Ser	Leu 435		Cys	Ile	Phe	Ala 440		Met	Val	Thr	Arg 445		Ala	Leu	
	Phe	Pro		Asp	Ser	Glu	Ile		Gln	Leu	Phe	Arq		Phe	Arg	Thr	
25		450				•	455	_				460					
	465	Gly	IIII	Pro	Asp	470	vai	vaı	Trp	Pro	475	vai	Thr	ser	Met	480	
		Tyr	Lvs	Pro	Ser		Pro	Lve	שיצים	Δla		Gln	Δαη	Dhe	Ser		
	пор	- 1 -	y		485			11 , 13	115	490	m 9	0111	nop		495	275	
30	Val	Val	Pro	Pro 500	Leu	qaA	Glu	Asp	Gly 505		Ser	Leu	Leu	Ser 510		Met	
	Leu	His	Tyr 515	Asp	Pro	Asn	Lys	Arg 520	Ile	Ser	Ala	Lys	Ala 525	Ala	Leu	Ala	
35	His	Pro 530	Phe	Phe	Gln	Asp	Val 535	Thr	Lys	Pro	Val	Pro 540	His	Leu	Arg	Leu	
		,	(2)	INI	FORM	ATIO1	V FOI	R SE	QI Ç	NO:	116:						
		į)	i) SI	EQUE	NCE (CHAR	ACTEI	RIST:	ICS:								٠
40							2 bas	•	airs								
							ic a										
							s: s: inea:	_	2				·				
4=																	
45				OLEC		TYPI	E: cl	AMC									
			(A)	MAN	ME/KI	EY: (Codi	ng Se	eque	nce							
50							RMAT										
		(ż	ci) S	EQUI	ENCE	DES	CRIP	rion	: SE	Q ID	NO:	116:					
	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTG	CCC	ATC	CTG	48
55	Met 1	Val	Ser		Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu	

5															TCC Ser		96
														•	TTC Phe		144
10						_									ACC Thr		192
15															ATG Met		240
20															CAG Gln 95		288
25	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	GCC Ala	Glu	336
	Val	Lys	Phe 115	Glu	Gly	Asp	Thr	Leu 120	Val	Asn	Arg	Ile	Glu 125	Leu	AAG Lys	Gly	384
30	Ile	Asp 130	Phe	Lys	Glu	Asp	Gly 135	Asn	Ile	Leu	Gly	His 140	Lys	Leu	GAG Glu	Tyr	432
35	Asn 145	Tyr	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	Asp	Lys	Glņ	AAG Lys	Asn 160	480
40	Gly	Ile	Lys	Val	Asn 165	Phe	Lys	Ile	Arg	His 170	Asn	Ile	Glu	Asp	GGC Gly 175	Ser	528
45	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	GAC Asp	Gly	576
															GCC Ala		624
50															GAG Glu		672
55								-							AAG Lys		720

5															CGA Arg 255		768
															GTC Val		816
10															TTC Phe		864
15															CAG Gln		912
20	Ser 305	Gly	Asp	Phe	Tyr	Asp 310	Leu	Tyr	Gly	Gly	Glu 315	Lys	Phe	Ala	ACT Thr	Leu 320	960
25	Thr	Glu	Leu	Val	Glu 325	Tyr	Tyr	Thr	Gln	Gln 330	Gln	Gly	Val	Leu	CAG Gln 335	Asp	1008
	Arg	Asp	Gly	Thr 340	Ile	Ile	His	Leu	Lys 345	Tyr	Pro	Leu	Asn	Cys 350	TCC Ser	Asp	1056
30	Pro	Thr	Ser 355	Glu	Arg	Trp	Tyr	His 360	Gly	His	Met	Ser	Gly 365	Gly	CAG Gln	Ala	1104
35															GTG Val		1152
40															AGT Ser		1200
45															ATC Ile 415		1248
															ACC Thr		1296
50															ATT Ile		1344
55															GCC Ala		1392

5						GAC Asp 470											1440
J						GAT Asp											1488
10	CAC	አረሞ	mma	C2 C		CNC	an a	ama			mma	a. a				<u> </u>	
						CAG Gln											1536
15						AAC Asn											1584
20	CCC Pro	TTT Phe 530	GAC Asp	CAC His	AGC Ser	CGA Arg	GTG Val 535	ATC Ile	CTG Leu	CAG Gln	GGA Gly	CGG Arg 540	GAC Asp	AGT Ser	AAC Asn	ATC Ile	1632
25						ATC Ile 550											1680
						GCT Ala											1728
30						GAC Asp											1776
35						ACC Thr											1824
40						CCC Pro											1872
45						TGC Cys 630											1920
45						TCC Ser											1968
50						TAC Tyr											2016
55	GAG Glu	CCT Pro	GGG Gly 675	GGT Gly	GTC Val	CTC Leu	AGC Ser	TTC Phe 680	CTG Leu	GAC Asp	CAG Gln	ATC Ile	AAC Asn 685	CAG Gln	CGG Arg	CAG Gln	2064

5												CAC His 700					2112
												ATG Met					2160
10												ATC Ile					2208
15	Gln	Met	Val	Arg 740	Ala	Gln	Arg	Ser	Gly 745	Met	Val	CAG Gln	Thr	Glu 750	Ala	Gln	2256
20												ATT Ile					2304
25												CAG Gln 780					2352
												GCC Ala					2400
30											Val	TAT Tyr					2448
35										Lys		CAG Gln			Ala		2496
40		GAG Glu				,						TGA		<i>,</i> .		•	2532
			(2) IN	FORM	ATIO	n fo	R SE	Q ID	NO:	117:						
45		((A) (B) (C)	EQUE LEN TYP STR	GTH: E: a ANDE	843 mino DNES	ami aci S: s	no a d ingl	cids								
50			ii)	TOP MOLE RAGM	CULE	TYP	E: p	rote									
55												117:		_		•	
	Met	. Val	Ser	Lys	Gly	Glu	Glu	Lev	ı Phe	e Thi	Gly	/ Val	. Val	Pro	ıl.	e Leu	0.4

	1				5					10					15	
		Glu	Leu	Asp 20	_	qaA	Val	Asn	Gly 25		Lys	Phe	Ser	Val 30	-	Gly
5	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
• .	Leu 65	Thr	Tyr	Gly	Val	Gln 70	Cys	Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys 80
10		His			85					90					95	
:		Thr		100					105					110		
15		Lys	115	•	_	_		120			_		125			
		Asp 130					135					140				
00	145	Tyr				150					155					160
20	-	Ile	-		165				-	170					175	
		Val		180		•			185					190		
25		Lys	195					200					205			
		210 Thr					215	_	_			220				
	225				_	230			_		235					240
30	-	Leu	_		245		•			250	_	_			255	
		Ser		260					265					270		
35	-	Ser	275					280	_	_			285	_		
		290 Gly		_			295					300				
40	305	-				310		- ·	_	_	315					320 Asp
40					325					330					335	Asp
	_	_	_	340					345	_				350		Ala
45			355					360	_				365			Arg
·		370					375	_			_	380				Asp
•	385					390		-			395					400
50			_		405					410					415	
				420					425					430		Phe
55	-		435					440					445			Glu
	Glu	Ala	Ser	Gly	Ala	Phe	Val	Tyr	Leu	Arg	Gln	Pro	Tyr	Tyr	Ala	Thr

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219

		450					455					460				
	Arg 465	Val	Asn	Ala	Ala	Asp 470	Ile	Glu	Asn	Arg	Val 475	Leu	Glu [.]	Leu	Asn	Lys 480
5					485	Asp			_	490	•		-		495	
-				500		Gln			505					510		
			515			Asn		520		•	_	_	525			
10		530				Arg	535					540				
	545					Ile 550					555					560
15					565	Ala				570					575	
				580		Asp			585					590		
			595			Thr		600				_	605	_		_
20		610			•	Pro	615					620		•		
	625					Cys 630				_	635			_	_	640
25					645	Ser			_	650	_	-			655	
				660		Tyr			665					670		
		·	675			Leu		680	•	_			685		_	
30		690				Ala	695					700	,-			_
	705					Thr 710					715					720
35					725	Leu	, -	-	_	730	_			-	735	
				740		Gln	_		745					750		
			755			Val		760					765			
40		770				Leu	775			_	_	780				
	785					Pro 790				_	795					800
45					805	Lys				810					815	
				820		Glu			825			Gln	Arg	Ser 830	Ala	Asp
•	Lys	Glu	Lys 835	Ser	Lys	Gly	Ser	Leu 840	Lys	Arg	Lys					
50																

(2) INFORMATION FOR SEQ ID NO:118:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2562 base pairs
- (B) TYPE: nucleic acid

55

(C) STRANDEDNESS: single

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220

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

5

(A) NAME/KEY: Coding Sequence

(B) LOCATION: 1...2559

(D) OTHER INFORMATION:

10		(2	xi) 8	SEQUI	ENCE	DESC	CRIP	NOI1	SEC	OID	NO:	118:						
					GGG Gly 5											GCA Ala		48
15					AAG Lys													96
20					AAC Asn													144
25					CAT His													192
30					GAG Glu													240
35					CAG Gln 85													288
					CCG Pro													336
40					ATG Met													384
45					TGG Trp													432
50					CTT Leu													480
55					AGG Arg 165											GGA Gly	•	528
	CGC	TAC	ACA	GTG	GGT	GGT	TTG	GAG	ACC	TŢC	GAC	AGC	CTC	ACG	GAC	CTG		576

										44 1							
	Arg	Tyr	Thr	Val 180	Gly	Gly	Leu	Glu	Thr 185	Phe	Asp	Ser	Leu	Thr 190		Leu	
	СТД	GAG	СДТ	שידיכ	AAG	AAG	ACG	GGG	אייי ע	GAG	GAG	GCC	יייי	CCC	GCC	աար	624
5					Lys												024
			195		-,-	-,-		200					205	011			
•																	•
	GTC	TAC	CTG	CGG	CAG	CCG	TAC	TAT	GCC	ACG	AGG	GTG	AAT	GCG	GCT	GAC	672
	Val	Tyr	Leu	Arg	Gln	Pro	Tyr	Tyr	Ala	Thr	Arg	Val	Asn	Ala	Ala	Asp	
10		210					215					220					
		~~~	220	CCN	ama.	mma	~~~	-									
					GTG Val												720
	225	Gru	Mali	Arg	vaı	230	GIU	ьeu	ASII	пув	235	GIII	GIU	ser	GIU	Asp 240	•
15						25,0					233					240	
	ACA	GCC	AAG	GCT	GGC	TTC	TGG	GAG	GAG	TTT	GAG	AGT	TTG	CAG	AAG	CAG	768
					Gly												
					245					250					255		
20					TTG												816
	GIU	vai	ьуs	260	Leu	uir	GIN	Arg	265	GIU	GIY	GIN	Arg	270	GIU	Asn	
				200					265					270		*	
	AAG	GGC	AAG	AAC	CGC	TAC	AAG	AAC	ATT	CTC	CCC	TTT	GAC	CAC	AGC	CGA	. 864
25					Arg												
		*	275					280					285				
																-	
				_	GGA												912
30	vaı	290	Leu	GIN	Gly	Arg	Asp 295	ser	Asn	TTE	Pro	_	ser	Asp	тут	TTE	
50		290			•		295					300					
	AAT	GCC	AAC	TAC	ATC	AAG	AAC	CAG	CTG	CTA	GGC	CCT	GAT	GAG	AAC	GCT	960
					Ile												
	305					310					315		_			320	•
35																	•
					GCC												1008
	Lys	Thr	Tyr	IIe	Ala	Ser.	GIn	Gly	Cys		Glu	Ala	Thr	Val		Asp	
					325					330					335		
40	TTC	TGG	CAG	ATG	GCG	TGG	CAG	GAG	AAC	AGC	CGT	GTC	ATC	GTC	ATG	ACC	1056
					Ala									1			
		_		340		_			345		_			350			
														,			
					GAG												1104
45	Thr	Arg		Val	Glu	Lys	Gly		Asn	Lys	Cys	Val		Tyr	Trp	Pro	
			355					360					365				•
	GAG	GTG	GGC	АТС	CAG	ССТ	GCT	ידעיד	GGG	CCC	тас	тСт	стс	ACC	AAC	TGC	1152
					Gln												1100
50		370	4			٠ ح	375	- 3 =	1		- x <b>-</b>	380		<b>_</b>			
					ACA												1200
		Glu	His	Asp	Thr		Glu	Tyr	Lys	Leu	_	Thr	Leu	Gln	Val		
55	385					390					395					400	
55	CCG	СТС	GAC	ייממ	GGA	GAC	ርጥር	ייייי ע	CGC	GNG.	איזיר	TGC	ሮእሞ	ጥለር	CAG	ጥልሮ	1248
				- 14 1.4	JUA		-10	WII.		GAG	WI.C	100	CNI	INC	CAU		1240

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										222		٠					
	Pro	Leu	Asp	Asn	Gly 405	Asp	Leu	Ile	Arg	Glu 410	Ile	Trp	His	Tyr	Gln 415	Tyr	
5															GTC Val		1296
10															CAC His		1344
																ACC Thr	1392
15															GGC Gly		1440
20															GCG Ala 495		1488
25															TAC Tyr		1536
30															GTC Val		1584
						Gln									TAT		1632
35		Ala				Ala	His		Lys	Ala	Ser		Thr		TCC Ser		1680
40															AGG Arg 575		1728
45															AAG Lys		1776
50															GCC Ala		1824
															TTC Phe		1872
55	GGG	GTG	GTG	CCC	ATC	CTG	GTC	GAG	CTG	GAC	GGC	GAC	GTA	AAC	GGC	CAC	1920

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										ZZJ							
	Gly 625	Val	Val	Pro	Ile	Leu 630	Val	Glu	Leu	Asp	Gly 635	Asp	Val	Asn	Gly	His 640	
5				GTG Val													1968
10				AAG Lys 660													2016
45				GTG Val													2064
15				CAC His													2112
20				GTC Val													2160
25				CGC Arg													2208
30				CTG Leu 740													2256
				CTG Leu													2304
35				CAG Gln													2352
40				GAC Asp													2400
45				GGC Gly													2448
50				TCC Ser 820													2496
				CTG Leu													2544
55	GAC	GAG	CTG	TAC	AAG	TAA											2562

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Asp Glu Leu Tyr Lys 850

```
5
               (2) INFORMATION FOR SEQ ID NO:119:
            (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 853 amino acids
              (B) TYPE: amino acid
10
              (C) STRANDEDNESS: single
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: protein
            (v) FRAGMENT TYPE: internal
15
           (xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:
      Met Leu Ser Arg Gly Trp Phe His Arg Asp Leu Ser Gly Leu Asp Ala
      Glu Thr Leu Leu Lys Gly Arg Gly Val His Gly Ser Phe Leu Ala Arg
20
      Pro Ser Arg Lys Asn Gln Gly Asp Phe Ser Leu Ser Val Arg Val Gly
                                  40
      Asp Gln Val Thr His Ile Arg Ile Gln Asn Ser Gly Asp Phe Tyr Asp
25
      Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Thr Glu Leu Val Glu Tyr
                          70
      Tyr Thr Gln Gln Gln Gly Val Leu Gln Asp Arg Asp Gly Thr Ile Ile
      His Leu Lys Tyr Pro Leu Asn Cys Ser Asp Pro Thr Ser Glu Arg Trp
30
                                      105
      Tyr His Gly His Met Ser Gly Gly Gln Ala Glu Thr Leu Leu Gln Ala
                                  120
      Lys Gly Glu Pro Trp Thr Phe Leu Val Arg Glu Ser Leu Ser Gln Pro
35
                              135
      Gly Asp Phe Val Leu Ser Val Leu Ser Asp Gln Pro Lys Ala Gly Pro
                          150
      Gly Ser Pro Leu Arg Val Thr His Ile Lys Val Met Cys Glu Gly Gly
                                          170
40
      Arg Tyr Thr Val Gly Gly Leu Glu Thr Phe Asp Ser Leu Thr Asp Leu
                                      185
      Val Glu His Phe Lys Lys Thr Gly Ile Glu Glu Ala Ser Gly Ala Phe
                                  200
      Val Tyr Leu Arg Gln Pro Tyr Tyr Ala Thr Arg Val Asn Ala Ala Asp
45
                              215
      Ile Glu Asn Arg Val Leu Glu Leu Asn Lys Lys Gln Glu Ser Glu Asp
                          230
```

224

Thr Ala Lys Ala Gly Phe Trp Glu Glu Phe Glu Ser Leu Gln Lys Gln

Glu Val Lys Asn Leu His Gln Arg Leu Glu Gly Gln Arg Pro Glu Asn

Asn Ala Asn Tyr Ile Lys Asn Gln Leu Leu Gly Pro Asp Glu Asn Ala

295

265 Lys Gly Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Ser Arg 280 Val Ile Leu Gln Gly Arg Asp Ser Asn Ile Pro Gly Ser Asp Tyr Ile

250

245

50

	205					310					215					320
	305	ጥኮ~	Tyr	Tla	715	_	Gln	Gly	Cres	T.OU	315	<b>λ</b> 1 α	Thr	W-1	λcn	-
	пуз	TILL	TYL	116	325	BCI	GIII	Gry	Сув	330	GIU	Ala	1111	Val	335	App
	Phe	Tro	Gln	Met		Trp	Gln	Glu	Asn		Ara	Val	Tle	Val		Thr
5				340					345		5			350		
	Thr	Arq	Glu		Glu	ayı	Gly	Arq		Lys	Cys	Val	Pro		Trp	Pro
		_	355			•	•	360			•		365	. •		
	Glu	Val	Gly	Met	Gln	Arg	Ala	Tyr	Gly	Pro	Tyr	Ser	Val	Thr	Asn	Cys
		370					375					380				
10	Gly	Glu	His	Asp	Thr	Thr	Glu	Tyr	Lys	Leu	Arg	Thr	Leu	Gln	Val	Ser
	385					390		_			395				_	400
	Pro	Leu	qaA	Asn	_	Asp	Leu	Ile	Arg		Ile	Trp	His	Tyr		Tyr
	•	0		D	405	174.	<b>~1</b>	77_7	D	410	<b>~</b> 1	D	<b>01.</b>	<b>~1</b>	415	T 011
15	ьeu	Ser	Trp	420	Asp	HIS	GIĀ	vaı	425	Ser	GIU	Pro	GIY	430	vaı	neu
13	Car	Dhe	Leu		Gln	Tle	Aen	Gln		Gln	Glu	Ser	Len		His	Δla
	501	11.0	435	шр	02			440	9	0111	014	<b>D</b> C1	445			
	Glv	Pro	Ile	Ile	Val	His	Cys		Ala	Gly	Ile	Glv		Thr	Gly	Thr
		450					455		•	•		460	_		•	
20	Ile	Ile	Val	Ile	Asp	Met.	Leu	Met	Glu	Asn	Ile	Ser	Thr	Lys	Gly	Leu
	465					470					475					480
	Asp	Cys	qaA	Ile	_	Ile	Gln	Lys	Thr		Gln	Met	Val	Arg		Gln
	_	_			485					490	_	_			495	
25	Arg	Ser	Gly			GIn	Thr	Glu		Gln	Tyr	Lys	Phe		Tyr	Val
25	חות	ם ד	Ala	500		Tla	Glu	Thr	505	Lare	Lare	Lare	T.611	510	17a ]	T.em
	Ald	116	515	GIII	PHE	116	Giu	520	TIII	цуь	пур	пув	525	Gru	vai	neu
	Gln	Ser	Gln	Lvs	Glv	Gln	Glu		Glu	Tvr	Glv	Asn		Thr	Tyr	Pro
		530		-2 -	2		535			-1-	2	540			•	
30	Pro	Ala	Met	Lys	Asn	Ala	His	Ala	Lys	Ala	Ser	Arg	Thr	Ser	Ser	Lys
	545					550					555					560
	His	Lys	Glu	Asp			Glu	Asn	Leu	His	Thr	Lys	Asn	Lys		Glu
				_	565		_	_		570	_		<b>-</b>		575	<b>01</b>
25	GIu	гля	Val	-	ьуѕ	GIn	Arg	ser		Asp	Lys	GIU	гла	590	гув	GIY
35	Sar	T.011	Larg	580	Lare	Ara	Tle	T.e.u	585	Cer	Thr	Val	Pro		Δla	Arg
	Ser	шец	595	nr 9	шуо	n. y	110	600	GIII	JCI	1111	Val	605	9	niu	****9
	Asp	Pro	Pro	Val	Ala	Thr	Met		Ser	Lys	Gly	Glu		Leu	Phe	Thr
	•	610					615			-	•	620				
40	Gly	Val	Val	Pro	Ile	Leu	Val	Glu	Leu	Asp	Gly	Asp	Val	Asn	Gly	His
	625					630					635					640
	Lys	Phe	Ser	Val		Gly	Glu	Gly	Glu	_	Asp	Ala	Thr	Tyr		Lys
	_	_,	_		645	_,	_	e1		650	_				655	
45	Leu	Thr	Leu	660 гуз	Pne	116	Cys	Thr	665	GIY	гàз	ьeu	Pro	670	PIQ	Trp
45	Pro	Thr	T.e.11		Thr	Thr	ī.e.u	Thr		Gly	Val	Gln	Cve		Ser	Arg
	PIO	1111	675	vai	1111	1111	LCu	680	ıyı	Gry	· var	0.111	685	1110	501	9
	Tvr	Pro		His	Met	Lvs	Gln		Asp	Phe	Phe	Lvs		Ala	Met	Pro
	-1-	690				•	695					700				
50	Glu	Gly	Tyr	Val	Gln	Glu	Arg	Thr	Ile	Phe	Phe	Lys	Asp	Asp	Gly	Asn
	705					710					715					720
	Tyr	Lys	Thr	Arg		Glu	Val	Lys	Phe		Gly	Asp	Thr	Leu		Asn
	_		<b>4.</b> 3	<b>-</b> .	725	<b>~</b> 3			_,	730	~ ?	<b>.</b>	<b>~</b> 3	<b>7</b>	735	
E.F.	Arg	11e	Glu		туѕ	GIY	тте	Asp		гув	GIU	qaA	GIY	750		Leu
55	۵۱۰۰	ui.	Tare	740	Gliv	ጥህም	V ~~	Tr	745	Cer	pic	Aen	ו פון			Met
	GTA	urs.	nλρ	Tie u	JIU	TAT	usil	TAL	Wall	261	1112	VOII	val	1 y 1	116	

			755					760					765						
•	Ala	Asp 770		Gln	Lys	Asn	Gly 775	Ile	Lys	Val	Asn	Phe 780	Lys	Ile	Arg	His			
5	Asn 785	Ile	Glu	Asp	Gly	Ser 790	Val	Gln	Leu	Ala			Tyr	Gln	Gln				
Ū		Pro	Île	Gly			Pro	Val	Leu			Asp	Asn	His	Tyr	800 Leu			
	Ser	Thr	Gln	Ser	805 Ala	Leu	Ser	Lys	Asp	810 Pro		Glu	Lys	Arg	815 Asp	His			
10	Met	Val	Leu	820 Leu	Glu	Phe	Val	Thr	825 Ala	Ala	Glv	Ile	Thr	830 Leu	Glv	Met			
			835	Tyr				840			1		845		,				
		850		-72	шуз											•			
15	•		(2)	) INI	FORM	OITA	v FOI	R SE	Q IĎ	NO:	120:								
		. (:	i) SI	EQUEI	NCE (	CHAR	ACTE	RIST:	ICS:										
				LENG				-	airs								•		
20			(C)	STRA	ANDE	ONES	3: s:	ingl	е										
														•.			٠		
				MOLE( FEAT		TYPI	s: Cl	ONA .											
25			(A)	IAN (	ME/KI	EY: (	Codin	ng Se	equei	nce									
				LOC OTI															
30		(3	xi) s	SEQUI	ENCE	DESC	CRIPT	rion	: SEC	O ID	NO:	120:							
•	AТG			AAG									ama	ccc	አጥሮ	OTTC		48	
	Met			Lys	Gly					Thr					Ile			40	
35	.1				5					10					15				
				GAC Asp														96	
				20					25					30					
40				GGC Gly													1	44	
		2	35	1				40	Cry	,	204		45	275		110			
				GGC													. 1	.92	
45	Cys	50	Thr	Gly	rys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr		١	
	CTG	ACC	TAC	GGC	GTG	CAG	TGC	TTC	AGC	CGC	TAC	CCC	GAC	CAC	ATG	AAG	. 2	40	
50				Gly															
		CAC	GAC	TTC	ጥጥር		TOO	GCC	አ መረግ	ccc		aca	ma ~	ama	CA C		_	. 0.0	
				Phe	Phe					Pro					Gln		2	8.8	
55					85					90					95				
	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	GCC	GAG	3	36	226
																			ب. ا

										~~ '								
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu		
	GTG	DAG	TTC	GAG	GGC	GAC	ACC	СТС	GTG	אאר	CGC	ATC	GAG	СТС	AAG	GGC	3	84
5												Ile						•
Ū	, u	_, _	115		<b>U</b> -1			120	• • • • • • • • • • • • • • • • • • • •		9		125		_,_	0-7		
	አመር	CAC	ጥጥር	አአሮ	CAC	CNC	ccc	7 7 C	אודיכי	CTC	000	CAC	ת ת ת	ama	CAC	ሞአር	4	32
			_									CAC His					*	32
10	116	130	FIIC	шyз		vaħ	135	WPII	TIE	шец	Gry	140	шуъ	пец	GIU	T Y T		
		150					133					140						
	AAC	TAC	AAC	AGC	CAC	AAC	GTC	TAT	ATC	ATG	GCC	GAC	AAG	CAG	AAG	AAC	4	80
	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	Ala	Asp	Lys	Gln	Lys	naA		
	145					150					155					160		
15																		
												ATC					5	28
	Gly	Ile	Lys	Val		Phe	Lys	Ile	Arg		Asn	Ile	Glu	Asp		Ser		
					165					170					175			
20	GTG	CAG	CTC	GCC	GAC	CAC	TAC	CAG	CAG	AAC	ACC	CCC	ATC	GGC	GAC	GGC	5	76
												Pro						
				180	•		•		185					190	-	-		
	CCC	GTG	CTG	CTG	CCC	GAC	AAC	CAC	TAC	CTG	AGC	ACC	CAG	TCC	GCC	CTG	6	24
25	Pro	Val		Leu	Pro	Asp	Asn	His	Tyr	Leu	Ser	Thr		Ser	Ala	Leu		
			195					200					205					
	AGC		GAC	כככ	אאר	GAG	DAG	CGC	СУТ	ראכ	ΔΤΩ	GTC	СТС	СТС	GAG	ጥጥር	6	72
					•							Val					. •	
30		210					215		<u>F</u> -			220						
	GTG	ACC	GCC	GCC	GGG	ATC	ACT	CTC	GGC	ATG	GAC	GAG	CTG	TAC	AAG	TCC	7	20
		Thr	Ala	Ala	Gly	Ile	Thr	Leu	Gly	Met	Asp	Glu	Leu	Tyr	Lys			
0.5	225					230					235					240		
35	003	ama	707	m/m	OG 3	COM	~ ~ ~	aam	maa.	7 7 C	maa	200	N MC	CNC	ccc	ccc	-	68
												ACC Thr					•	00
	Gry	пец	Arg	Ser	245	MIG	GIII	MIA	Set	250	Ser	1111	MEL	GIU	255	FIO		
						•				230								
40	CCG	GGG	CTG	CGG	CCG	GGC	GCG	GGC	GGG	CCC	TGG	GAG	ATG	CGG	GAG	CGG	8	16
	Pro	Gly	Leu	Arg	Pro	Gly	Ala	Gly	Gly	Pro	Trp	Glu	Met	Arg	Glu	Arg		
				260					265					270				
		~~~												~~ m		<b>a</b> > >	,	
1 <i>E</i>												TAC						364
45	neu	GIY	275	GIY	GIY	Pne	GIY	280	vaı	Cys	Leu	Tyr	285	HIS	Arg	Giu		
			2/5					280					205					
	CTT	GAT	CTC	AAA	ATA	GCA	ATT	AAG	TCT	TGT	CGC	CTA	GAG	CTA	AGT	ACC	9	912
•												Leu					•	
50		290		-			295	•		•		300						
												ATT					9	960
	-	Asn	Arg	Glu	Arg	_	Cys	His	Glu	Ile		Ile	Met	Lys	Lys			
E E	305					310					315					320		
55	ממ	ጥልጥ	פרת	ידעע	ርጥጥ	Стл	מממ	GCC	ستاس	ת עים	تشش	ССФ	עעט	ממט	ב) להלה	AAT	1 (800
	AMC	CMI	GCC	WYI	CII	CIM	AAG	GCC	101	GAI	GII	1	GAA	GAA.	.10	LMJI	٠. ٠	, ,
																		4

									'								
·	Asn	His	Ala	Asn	Val 325	Val	Lys	Ala	Сув	Asp 330	Val	Pro	Glu	Glu	Leu 335	Asn	
	АТТ	TTG	ATT	CAT	GAT	GTG	ССТ	CTT	CTA	GCA	ATG	GAA	TAC	TGT	TCT	GGA	1056
5					Asp												
				340					345					350		•	
•	GGA	GAT	CTC	CGA	AAG	CTG	CTC	AAC	AAA	CCA	GAA	TAA	TGT	TGT	GGA	CTT	1104
	Gly	Asp	Leu	Arg	Lys	Leu	Leu	Asn	Lys	${\tt Pro}$	Glu	Asn	Cys	Cys	Gly	Leu	
10			355					360					365				
					ATA												1152
	Lys		Ser	Gin	Ile	Leu		Leu	Leu	Ser	Asp		Gly	Ser	GIY	lle .	
15		370					375					380					
13	CGA	тат	TTG	САТ	GAA	AAC	AAA	ATT	АТА	САТ	CGA	GAT	СТА	AAA	CCT	GAA	1200
					Glu												
	385	•				390	•				395	. •		-		400	•
20					CAG												1248
	Asn	Ile	Val	Leu	Gln	qaA	Val	Gly	Gly		Ile	Ile	His	Lys		Ile	
					405					410					415		
	CNT	CTC	GGA	ጥእጥ	GCC	אאא	ርስጥ	CTT	ርስጥ	מאם.	CCN	λCT	CTC	יייביייי	אכא	TOTE .	1296
25.					Ala												1230
				420		-,, -	E		425		,			430			
,							-										
					CTG												1344
	Phe	Val	_	Thr	Leu	Gln	Tyr		Ala	Pro	Glu			Glu	Asn	Lys	
30			435				•	440				,	445				
	ССТ	TAC	ACA	GCC	ACT	GTT	САТ	ידביד	TGG	AGC	արդա	GGG	ACC	ATG	GTA	արդար	1392
					Thr												
•		450					455	-	-			460					
35																	
					GGA												1440
		Cys	Ile	Ala	Gly	_	Arg	Pro	Phe	Leu		His	Leu	Gln	Pro		
	465					470					475					480	
40	ACC	TGG	CAT	GAG	AAG	ATT	AAG	AAG	AAG	GAT	CCA	AAG	тст	АТА	TTT	GCA	1488
.0					Lys												
		•			485		•	•	•	490		•	-		495		
			•														
					TCA												1536
45	Cys	Glu	Glu		Ser	Gly	Glu	Val	_	Phe	Ser	Ser	His		Pro	Gln	
				500					505					510			
	כרא	ጥαα	AGC	ىئىش	ጥርጥ	ጀርጥ	מיזייף	מידים	מידא	CDV	ררר	ልጥር፤	GDD	מממ	ፓርር	CTA	1584
•					Cys												
50			515		-,, -			520					525	• • •	r		
					AAT												1632
	Gln		Met	Leu	Asn	Trp		Pro	Gln	Gln	Arg		Gly	Pro	Val	qaA	
E E		530					535					540					
55	ىئىنىك	ልሮሞ	יטיניינה	ממ	ר∡מ	רר.	D CD	ተርነጥ	יווינווינו	עידים	ጥጥኦ	אינים	ርልጥ	CAC	ው ጥተ	TTG	1680
	C11	AC 1	110	מאה	CHU	CCA	AGA	101	111	GTW	· · · · ·	AIG	Onl	CAC	47 I		2.00

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	Leu 545	Thr	Leu	Lys	Gln	Pro 550	Arg	Cys	Phe	Val	Leu 555	Met	Asp	His	Ile	Leu 560		
5		TTG Leu															1728	
10		TTT Phe			Pro												1776	
15		GAG Glu															1824	
15		ACA Thr 610															1872	
20		GAT Asp															1920	
25		AGT Ser															1968	
30		TGT Cys															2016	
25		CAG Gln															2064	
35		AAA Lys 690												_	_		2112	
40		AGT Ser															2160	
45		ATC Ile															2208	
50		AGC Ser															2256	
		ATA Ile													_		2304	
55	AAG	GCC	ATC	CAC	TAT	GCT	GAG	GTT	GGT	GTC	ATT	GGA	TAC	CTG	GAG	GAT	2352	229

	Lys	Ala 770	Ile	His	Tyr	Ala	Glu 775	Val	Gly	Val	Ile	Gly 780	Tyr	Leu	Glu	Asp		
5				TCT Ser													2400	
10				CGT Arg													2448	
4-				TAT Tyr 820													2496	
15				ACA Thr													2544	
20			Arg	GTG Val													2592	
25				CAG Gln													2640	•
30				ATC Ile													2688	
				AAA Lys 900													2736	
35				CGC Arg													2784	
40				TCA Ser									Glu				2832	
45				TGT Cys			Thr									CAA Gln 960	2880	
50				GAA Glu							His						2928	
										Ser					Asp	TGG	2976	
55	AGT	TGG	TTA	ACA	GAA	TGA							٠.				2994	230

```
Ser Trp Leu Thr Glu
995
```

55

```
5
               (2) INFORMATION FOR SEQ ID NO:121:
            (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 997 amino acids
              (B) TYPE: amino acid
10
              (C) STRANDEDNESS: single
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: protein
            (v) FRAGMENT TYPE: internal
15
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:
     Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
20
     Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
                                      25
     Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
     Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
25
     Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
                          70
     Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                                          90
30
     Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
                 100
                                      105
     Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
                                  120
     Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
35
                              135
     Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
                          150
                                              155
     Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                                          170
40
     Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
                                      185
     Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
                                  200
      Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
45
                              215
     Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
                          230
                                              235
     Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Glu Arg Pro
                      245
                                          250
50
     Pro Gly Leu Arg Pro Gly Ala Gly Gly Pro Trp Glu Met Arg Glu Arg
                                      265
     Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr Gln His Arg Glu
                                  280
     Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu Glu Leu Ser Thr
```

Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu

	305					310					315					320
	Asn	His	Ala	Asn	Val 325	Val	Lys	Ala	Cys	Asp 330	Val	Pro	Glu	Glu	Leu 335	Asn
5	Ile	Leu	Ile	His 340	Asp	Val	Pro	Leu	Leu 345	Ala	Met	Glu	Tyr	Cys 350	Ser	Gly
	-	_	355	_				360	-				365	Сўв	_	
* .	Lys	Glu 370	Ser	Gln	Ile	Leu	Ser 375	Leu	Leu	Ser	Asp	Ile 380	Gly	Ser	Gly	Ile
10	Arg 385	Tyr	Leu	His	Glu	Asn 390	Lys	Ile	Ile	His	Arg 395	Asp	Leu	Lys	Pro	Glu 400
	Asn	Ile	Val	Leu	Gln 405	Asp	Val	Gly	Gly	Lys 410	Ile	Ile	His	Lys	11e 415	Ile
15	•		_	420		_	_		425		-			Cys 430		
			435				_	440				•	445	Glu	•	
		450					455		_			460		Met		
20	465	-			_	470		-			475			Gln		480
•		_			485			_	-	490		-		Ile	495	
25	-			500		_			505		•			Leu 510		
			515		_			520					525	Asn		
		-530					535					540		Pro		
30	545					550					555			His		560
					565					570				Lys	575	
35				580			-		585					Gln 590		
			595			-		600					605	Leu		
40		610					615		-	_		620		Gln		
40	625	_				630		_		-	635			Leu		640
	-				645	_				650				Ser	655	
45				660					665					Leu 670		
•			675					680					685			
		690		_	_		695				_	700		Ala		
50	705					710					715			Lys		720
					725					730				Phe	735	
55	_			740					745		•			Met 750		
	Gly	Ile	Ser	ser	Glu	гàг	Met	Leu	Lys	Ala	Trp	Lys	Glu	Met	Glu	Glu

			755					760					765					
	Lys	Ala 770	Ile	His	Tyr	Ala	Glu 775	Val	Gly	Val	Ile	Gly 780	Tyr	Leu	Glu	Asp	•	
5	Gln 785		Met	Ser	Leu	His 790	Ala	Glu	Ile	Met	Gly 795	Leu	Gln	Lys	Ser	Pro 800		
		Gly	Arg	Arg	Gln 805		Asp	Leu	Met	Glu 810		Leu	Glu	Gln	Arg 815	Ala		
	Ile	qaA	Leu	Tyr 820		Gln	Leu	Lys	His 825		Pro	Ser	Asp	His 830		Tyr		
10	Ser	Asp	Ser 835		Glu	Met	Val	Lys 840		Ile	Val	His	Thr 845		Gln	Ser		
		Asp 850	Arg	Val	Leu	Lys	Glu 855		Phe	Gly	His	Leu 860		Lys	Leu	Leu		
15			Lys	Gln	Lys	Ile 870		Asp	Leu	Leu	Pro 875		Val	Glu	Val	Ala 880		
		Ser	Asn	Ile	Lys 885		Ala	qaA	Asn	Thr 890		Met	Phe	Met	Gln 895			
	Lys	Arg	Gln	Lys 900		Ile	Trp	His	Leu 905		Lys	Ile	Ala	Cys 910		Gln		
20	Ser	Ser	Ala 915		Ser	Leu	Val	Gly 920		Ser	Leu	Glu	Gly 925		Val	Thr		
	Pro	Gln 930	Thr	Ser	Ala	Trp	Leu 935		Pro	Thr	Ser	Ala 940	-	His	Asp	His		
25	Ser 945		Ser	Cys	Val	Val 950		Pro	Gln	Asp	Gly 955		Thr	Ser	Ala	Gln 960		
		Ile	Glu	Glu	Asn 965		Asn	Cys	Leu	Gly 970	His	Leu	Ser	Thr	Ile 975	Ile	•	
	His	Glu	Ala	Asn 980		Glu	Gln	Gly			Met	Met	Asn	Leu 990	Asp	Trp		
30	Ser	Trp	Leu 995	Thr	Glu				•									
			(2)	IN	FORM	ATIO	N FO	R SE	Q ID	NO:	122:			•				
35		(:	i) SI	QUE	NCE	CHAR	ACTE:	RIST	ICS:									
			(B)	TYP	E: n	299: ucle:	ic a	cid										
						DNES: Y: 1			е									
40		•	ii) N			TYP	E: c	AND										
•		(:	ix) I															
45		•	(B)	LO(CATI	EY: ON: INFO	1	2988	eque	nce								
		(:	xi) S	SEQU:	ENCE	DES	CRIP	TION	: SE	Q ID	NO:	122:						
50																GAG Glu		48
55																TAC Tyr		96

5	CAT His										144
J	 CTA Leu 50						_	_	_		192
10	AAG Lys										240
15	GAA Glu									_	288
20	 TGT Cys										336
25	 TGT Cys										384
	 TCT Ser 130										432
30	Lys Lys										480
35	 AAA Lys										528
40	TGT Cys								_		576
45	GAG Glu										624
	ATG Met 210										672
50	 CAG Gln					Lys					720
55	ATA Ile									Ser	768

				Gln					Cys					GAA Glu			816
5				260					265					270			
J	GAA	AAC	TGG	CTA	CAG	TTG	ATG	TTG	TAA	TGG	GAC	CCT	CAG	CAG	AGA	GGA	864
•														Gln			
			275					280		_	_		285		_	-	
10														GTA			912
	GIY		vaı	Asp	ьeu	Thr		гла	GIn	Pro	Arg		Phe	Val	Leu	Met	
		290					295					300					
	GAT	CAC	ATT	TTG	AAT	TTG	AAG	ATA	GTA	CAC	ATC	СТА	AAT	ATG	ACT	TCT	960
15														Met			
	305					310					315					320	
														CTT			1008
20	АТА	гур	TTE	TTE	325	Pne	Leu	Leu	Pro	330	Asp	Glu	ser	Leu		ser	
20										330					335		
	CTA	CAG	TCT	CGT	ATT	GAG	CGT	GAA	ACT	GGA	ATA	AAT	ACT	GGT	TCT	CAA	1056
														Gly			
				340					345			,		350			
25																	
														AAA			1104
	GIU	пеп	355	SEL	Giu	1111	Gry	360	Set	ьец	Asp	PIO	365	Lys	PIO	Ala	
•																	
30	TCT	CAA	TGT	GTT	CTA	GAT	GGA	GTT	AGA	GGC	TGT	GAT	AGC	TAT	ATG	GTT	1152
	Ser	Gln	Cys	Val	Leu	Asp	Gly	Val	Arg	Gly	Cys	Asp	Ser	Tyr	Met	Val	
		370					375	•				380					
	m a m	mmc	and the	C N M	777	» cm	222	3 OIII	Om s	m. m	<i>-</i>	000	aar	mmm	com	maa	1200
35														TTT Phe			1200
00	385	11Cu	- 110	мор	Lyb	390	בעם	1111	Vai	ıyı	395	GTÅ	FIO	FIIC	AIG	400	
														AGC			1248
	Arg	Ser	Leu	Ser	Asp	Cys	Val	Asn	Tyr	Ile	Val	Gln	Asp	Ser	Lys	Ile	
40					405					410					415		
	CNG	COUNT	CCA	ን/ ጥጥ	אידי <i>א</i>	CVG	CTC	CCT	מממ	CMC	maa	COTT	C 3 3	GCA	OTO:	CNC	1296
														Ala			1250
				420					425					430			
45	•																
														CAG			1344
•	Tyr	Val		Gly	Leu	Lys	Glu	_	Tyr	Ser	Arg	Leu		Gln	Gly	Gln	
		•	435					440					445				
50	AGG	GCA	GCA	ATG	TTA	AGT	СТТ	CTTT	4DA	ጥልጥ	ጥፈፈ	GCT	אאר	TTA	ACA	AAA	1392
														Leu			2002
	-	450					455			. –		460				-	
55														GCT			1440
55		Lys	Asn	Thr	Leu		Ser	Ala	Ser	Gln		Leu	Lys	Ala	ràs		
	465					470					475					480	

5	TTT Phe									1488
Ū	ATG Met									1536
10	 ATG Met				 	 				1584
15	CTG Leu 530									1632
20	AAG Lys									1680
25	CAG Gln									1728
	CAC His									1776
, 30	GTG Val									1824
35	AAG Lys 610									1872
40	GAA Glu									1920
45	ATG Met								_	1968
	TGT Cys						•			2016
50	GCA Ala								_	2064
55	CAT His 690									2112

5														GGC Gly			2160
•														AGT Ser			2208
10														GCC Ala 750			2256
15			_	_								Glu		TTC Phe		GGG Gly	2304
20														GGC Gly			2352
25	Phe 785	Ser	Val	Ser	Gly	Glu 790	Gly	Glu	Gly	Asp	Ala 795	Thr	Tyr	GGC Gly	ГÀЗ	Leu 800	2400
														CCC Pro			2448
30														AGC Ser 830			2496
35	Pro	Asp	His 835	Met	Lys	Gln	His	Asp 840	Phe	Phe	Lys	Ser	Ala 845	ATG Met	Pro	Glu	2544
40	Gly	Tyr 850	Val	Gln	Glu	Arg	Thr 855	Ile	Phe	Phe	Lys	Asp 860	Asp	GGC	Asn	Tyr	2592
45		Thr												GTG Val			2640
														ATC Ile			2688
50														ATC Ile 910			2736
55														CGC Arg			2784

5		GAG Glu 930															2832
		ATC Ile															2880
10		CAG Gln	-														2928
15		CTG Leu															2976
20		CTG Leu			TAA			\$ *									2991
			· (2)	INI	FORM	ATIOI	N FOI	R SE	Q ID	NO:	123:						
25		(i)	(A) (B) (C)	LENG TYPI STRA	ETH: E: at ANDEI	996 mino ONES	ACTEI amin acio S: s:	no ao i ingle	cids						• .		
30		(1	ii) N 7) FI	MOLE (CULE ENT	TYPI TYPE	E: p: : in	rote: terna	al	o ID	NO : :	123:					
35	Met	Glu			Pro					Gly			Gly	Pro		Glu	
	1 Met	Arg	Glu		5 Leu	Gly	Thr	Gly		10 Phe	Gly	Asn	Val	Cys	15 Leu	Tyr	
40	Gln	His	Arg 35	20 Glu	Leu	Asp	Leu	Lys	25 Ile	Ala	Ile	Lys	Ser		Arg	Leu	
	Glu	Leu 50		Thr	Lys	Asn	Arg 55		Arg	Trp	Cys	His 60		Ile	Gln	Ile	
45	Met 65		Lys	Leu	Asn	His 70	Ala	Asn	Val	Val	Lys 75	Ala	Cys	Asp	Val	Pro	
					85					90					95	Glu	
	_	•		100					105					110		naA	
50	-	-	115					120					125			Ile	
	-	130	_				135					140			•	Asp	•
55	Leu 145	_	Pro	Glu	Asn	Ile 150		Leu	Gln	Asp	Val 155		GIA	Lys	116	: Ile 160	
			Ile	Ile	Asp			Tyr	Ala	Lys			Asp	Gln	Gly	Ser	2

					165					170					175	
	Leu	Cys	Thr	Ser 180		Val	Gly	Thr	Leu 185		Tyr	Leu	Ala	Pro 190	Glu	Leu
5	Phe	Glu	Asn 195	Lys	Pro	Tyr	Thr	Ala 200	Thr	Val	Asp	Tyr	Trp 205	Ser	Phe	Gly
		210					215					220			His	
•	225					230					235				Pro	240
10					245					250					Ser 255	
				260					265					270	Pro	
15			275					280					285		Arg	
	-	290	• •				295				-	300			Leu	
	305	HIS	116	ьeu	ASII	310	БУБ	TTE	val	uis	315	пеп	ASII	Mec	Thr	320
20		-			325					330					His 335	
				340					345					350	Ser	
25			355					360					365		Pro	
		370	-			_	375		_	_		380			Met	
. * *	385			_	_	390					395				Ala	400
30	_				405					410					Lys 415	
				420					425					430	Val	
35	_		435					440					445		Gly	
	-	450					455					460			Thr	
	Met 465	Lys	Asn	Thr	Leu	470		Ala	ser	Gin	475		пÀв	Ala	Lys	480
40				*	485					490					495	Glu
		•	•	500					505					510		Lys
45	•		515					520					525			Gly
		530					535					540				Leu -
	545	_				550					555					Leu 560
50					565					570)				575	
				580					585					590		His
55	Thr	Val	Gln 595	Ser	Gln	Asp	Arg	Val 600		Lys	Glu	Leu	Phe 605		HIS	Leu
-	Ser	Lys	Leu	Leu	Gly	Cys	Lys	Gln	Lys	Ile	lle	Asp	Lev	Leu	Pro	Lys

		610					615					620				
	Val	Glu	Val	Ala	Leu	Ser	Asn	Ile	Lys	Glu	Ala	Asp	Asn	Thr	Val	Met
	625					630					635					640
	Phe	Met	Gln	Gly	Lys	Arg	Gln	Lys	Glu	Ile	Trp	His	Leu	Leu	Lys	Ile
5					645					650					655	
	Ala	Cys	Thr	Gln	Ser	Ser	Ala	Arg	Ser	Leu	Val	Gly	Ser	Ser	Leu	Glu
		-		660				_	665			_		670		
	Glv	Ala	Val	Thr	Pro	Gln	Thr	Ser	Ala	Trp	Leu	Pro	Pro	Thr	Ser	Ala
	4-7		675					680		•			685			
10	Glas	His		Hic	Ser	T.e.11	Ser		Val	Val	Thr	Pro		Asp	Glv	Glu
10	GIU		App	111.0	DCI	DCu	695	Cyb	VUI	vui		700	01		027	
	m)	690 Ser	7 J -	C1 5	Mat	T10		C1	A can	Lou	λcn.		Len	Glv	ui a	T.611
		ser	Ala	GIII	Mec		GIU	GIU	ASII	Leu		Cys	Den	GTÅ	UTS	
	705				•	710		_		~1	715	~ 7				720
	Ser	Thr	He	He		Glu	Ala	Asn	GIu		GIN	GIY	Asn	ser		Met
15					725			,	_	730	_			_	735	
	Asn	Leu	Asp	Trp	Ser	Trp	Leu	Thr	Glu	\mathtt{Trp}	Val	Pro	Arg	Ala	Arg	Asp
				740					745					750		
	Pro	Pro	Val	Ala	Thr	Met	Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly
			755					760					765			•
20	Val	Val	Pro	Ile	Leu	Val	Glu	Leu	Asp	Gly	Asp	Val	Asn	Gly	His	Lys
		770					775		_	_		780		•		
	Phe	Ser	Val	Ser	Glv	Glu	Glv	Glu	Glv	Asp	Ala	Thr	Tvr	Gly	Lys	Leu
	785	501			1	790	2				795		- 4	•	•	800
		Leu	T.ve	Dhe	Tle		Thr	Thr	Glv	Lvs		Pro	Val	Pro	Trp	
25	1111	пси	_,		805	C y L			- -7	810					815	
25	mb	Leu	17-3	.Th~		Len	Thr	There	Glv		Gln	Cve	Dhe	Ser		Tyr
	THE	ьеu	val		1111	Dea	1111	TYL	825	VOI	GIII	Cys	FIIC	830	n. g	
	_		TT 3	820	.	01	772 -	3		nh -	T	0	ח ות	-	Dro	0111
	Pro	Asp		мес	ьуs	GIN	HIS	_	Pne	Pne	гув	261		ויופנ	PIO	GIU
	_	_	835			_		840	_,	_,	_	_	845	a 3	3	
30	GIA	Tyr	vaı	GIn	GIU	Arg		тте	Pne	Pne	гÀг		Asp	GIY	ASII	Tyr
		850		_	_	_	855		_			860	_	•	_	_
	Lys	Thr	Arg	Ala	Glu		Lys	Phe	Glu	Gly		Thr	Leu	Val	Asn	
	865					870					875					880
	Ile	Glu	Leu	Lys	Gly	Ile	Asp	Phe	Lys	Glu	Asp	Gly	Asn	Ile	Leu	Gly
35					885					890					895	
	His	Lys	Leu	Glu	Tyr	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	Ala
				900					905					910		
	Asp	Lys	Gln	Lys	Asn	Gly	Ile	Lys	Val	Asn	Phe	Lys	Ile	Arg	His	Asn
	•	-	915	-		-		920				_	925			
40	Tle	Glu		Glv	Ser	Val	Gln		Ala	Asp	His	Tvr	Gln	Gln	Asn	Thr
, ,		930		1			935				-	940				
	Pro	Ile	Glv	Asn	Glv	Pro			ī.e.ı	Pro	Δsn			Tvr	Leu	Ser
	945		017	1100	01,	950				110	955			-1-		960
		Gln	802	ת 1 ת	Len		Laze	λen	Dro	Acn			Δra	Aen	His	
AE	Till	GIII	SET	AIA		SEL	пуъ	Mah	PIO			шув	n. 9	пор	975	
45			T	0 3.	965	77-7	m\	7.7	7. 7	970		mb		01. .		
	val	Leu	ьeu			val	inr	ATA			тте	THI	шeu			Mah
	_			980					985					990		
	Glu	Leu	_	Lys									*			
			995													
50																

(2) INFORMATION FOR SEQ ID NO:124:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1908 base pairs
 - (B) TYPE: nucleic acid

55

(C) STRANDEDNESS: single

241

(D)	TOPOLOGY:	linear
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(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence (B) LOCATION: 1...1905

(D) OTHER INFORMATION:

10	(xi)	SEQUENCE	DESCRIPTION:	SEO	TD	NO: 124:

10		()	ci) s	SEQUE	ENCE	DESC	RIPI	ION:	SEC) ID	NO : 1	124:					
		,-	,														
		GTG Val										•					48
	Met 1	Val	ser	пуъ	5 5	Giu	GIU	Leu	Phe	10	GIY	Val	vaı	PIO	15	пеп	
15																	
		GAG Glu															96
	vai	GIU	200	20	Cly	p	,		25		Ly S	1110	JCI	30		.	
		aaa	an a	000	a.m	000	N C C	ma a	000		ama	. 200	ama	220	mma	» ma	144
20		GGC Gly															144
			35	-				40					45	•			
	TGC	ACC	אככ	GGC	AAG	СТС	CCC	GTG	ccc	TGG	ccc	אככ	רידיר	GTG	ארכ	ACC	192
25		Thr															
		50					55					60					
	CTG	ACC	TAC	GGC	GTG	CAG	TGC	TTC	AGC	CGC	TAC	ccc	GAC	CAC	ATG	AAG	240
		Thr															
30	65					70					75					80	
	CAG	CAC	GAC	TTC	TTC	AAG	TCC	GCC	ATG	CCC	GAA	GGC	TAC	GTC	CAG	GAG	288
	Gln	His	Asp	Phe		Lys	Ser	Ala	Met		Glu	Gly	Tyr	Val		Glu	
35				٠.	85					90					95		
	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	GCC	GAG	336
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg	Ala	Glu	
				100					105					110			
40		AAG														_	384
	Val	Lys	Phe	Glu	Gly	Asp	Thr	Leu 120	Val	Asn	Arg	Ile	G1u 125	Leu	ьуs	GIA	
AE		GAC													_		432
45	шe	Asp 130	Pne	гув	GIU	Asp	135	ASII	TTE	Leu	GIY	140	пув	Lea	Giu	ıyı	
		TAC Tyr															480
50	145	TYL	ASII	SCI	111.5	150	Vai	+ y L	116	ricc	155	лэр	טעם	0111	2,5	160	
				ama					,				a. a	a. a	222	200	620
		ATC Ile															528
	1		-, -		165		_1 _		3	170				&-	175		
55	000	a	ama	999	020	~ ~ ~	ma	03 C	C3.C	n n ~	7.00	000	איייט	CCC	GNC	GGC	576
	GTG	CAG	CTC	GCC	GAC	CAC	TAC	CAG	CAG	AAC	ACC	CCC	ATC	GGC	GAC	300	5/6

	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly		
5							AAC Asn										624	
10							AAG Lys 215										672	
							ACT Thr										720	
15							CAA Gln										768	
20							TCC Ser										816	
25				Lys			CTC Leu										864	
30							CAC His 295										912	
							CCC Pro										960	
35							TAT Tyr										1008	
40							GTC Val										1056	
45							GCC Ala		Met							TTG Leu	1104	
50	_		Gly					Pro					Thr			GTC Val	1152	
		Asn					Glu					Gln				CAG Gln 400	1200	
55	ccc	GGC	CCG	TCG	GAG	CAC	ATA	GAG	CGC	CGG	GTC	TCC	TAA	' GCA	. GGA	GGC	1248	242

	Pro	Gly	Pro	Ser	Glu 405	His	Ile	Glu	Arg	Arg 410	Val	Ser	Asn	Ala	Gly 415	Gly	
5				CCC Pro 420													1296
10				GGT Gly												_	1344
15				GCG Ala													1392
13				GCA Ala													1440
20				GCT Ala													1488
25				TCA Ser 500											_		1536
30				GGG Gly													1584
0.5			Lys	GCC Ala													1632
35				GAG Glu													1680
40				CCC Pro							Thr					Lys	1728
45										Thr					Pro	AGC Ser	1776
50				Tyr					Arg					Leu		GAA Glu	1824
•			Lys					Lys					Ile			GCC Ala	1872
55	TTC	GTC	CAG	GAG	CTG	AGG	AAG	CGG	GGT	TÇI	ccc	TGA					1908 243

Phe Val Gln Glu Leu Arg Lys Arg Gly Ser Pro 625 630 635

5 (2) INFORMATION FOR SEQ ID NO:125:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 635 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 25 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 90 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 30 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 125 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 135 35 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 155 150 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 170 165 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 40 .185 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 200 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 45 215 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 235 Gly Leu Arg Ser Arg Ala Gln Ala Ser Met Ser Glu Thr Val Ile Met 250 245 Ser Glu Thr Val Ile Cys Ser Ser Arg Ala Thr Val Met Leu Tyr Asp 50 265 Asp Gly Asn Lys Arg Trp Leu Pro Ala Gly Thr Gly Pro Gln Ala Phe 280 Ser Arg Val Gln Ile Tyr His Asn Pro Thr Ala Asn Ser Phe Arg Val 295 55 Val Gly Arg Lys Met Gln Pro Asp Gln Gln Val Val Ile Asn Cys Ala

	305					310					315					320
			Arg		325					330					335	
5	-	_	Asp	340					345					350		
	Asp	Ala	Ala 355	Gln	Phe	Ala	Ala	Gly 360	Met	Ala	Ser	Ala	Leu 365	Glu	Ala	Leu
•		370	Gly	_			375					380				
10	385		Gly			390					395				•	400
•		_	Pro		405					410					415	
15			Ala	420					425					430		
		•	Pro 435					440					445			
		450	Ala				455					460				
20	465		Ala	•		470		•			475					480
			Ala		485		_			490					495	
25			Ala	500					505					510		
		-	Gly 515					520					525			
		530	Lys				535					540				
30	545		Gln			550					555					560
		_	Arg		565					570					575	
35			Ser	580					585					590		
			Asp 595					600	,				605			
		610		-		٠.	615					620		Ile	GIu	Ala
40	Phe 625		Gln	Glu	Leu	Arg 630	_	Arg	Gly	Ser	635					
			(2) IN	FORM	ATIC	N FC	R SE	Q ID	NO:	126:				٠	
45		(i) s	_							-					
			(B)	TYP	GTH: E: n	ucle	ic a	cid		,						
					ANDE			_	.е							
50			ii) ix)				E: c	DNA								
55					ME/K	ON:	1	. 1326	-	ence						
			, _		1117	TAIR	N N N P	DT-01-								

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

5	ATG Met 1	GTG Val	AGC Ser	AAG Lys	GGC Gly 5	GAG Glu	GAG Glu	CTG Leu	TTC Phe	ACC Thr 10	GGG Gly	GTG Val	GTG Val	CCC Pro	ATC Ile 15	CTG Leu	4	. 8	
10	GTC Val	GAG Glu	CTG Leu	GAC Asp 20	GGC Gly	GAC Asp	GTA Val	AAC Asn	GGC Gly 25	CAC His	AAG Lys	TTC Phe	AGC Ser	GTG Val 30	TCC Ser	GGC Gly	. <u>9</u>	96	
15	GAG Glu	GGC Gly	GAG Glu 35	GGC Gly	GAT Asp	GCC Ala	ACC Thr	TAC Tyr 40	GGC Gly	AAG Lys	CTG Leu	ACC Thr	CTG Leu 45	AAG Lys	TTC Phe	ATC Ile	14		
13 ,	TGC Cys	ACC Thr 50	ACC Thr	GGC Gly	AAG Lys	CTG Leu	CCC Pro 55	GTG Val	CCC Pro	TGG Trp	CCC Pro	ACC Thr 60	CTC Leu	GTG Val	ACC Thr	ACC Thr	. 19	92	
20	CTG Leu 65	ACC Thr	TAC Tyr	GGC Gly	GTG Val	CAG Gln 70	TGC Cys	TTC Phe	AGC Ser	CGC Arg	TAC Tyr 75	CCC	GAC Asp	CAC His	ATG Met	AAG Lys 80	24	40	
25	CAG Gln	CAC His	GAC Asp	TTC Phe	TTC Phe 85	AAG Lys	TCC Ser	GCC Ala	ATG Met	CCC Pro 90	GAA Glu	GGC	TAC Tyr	GTC Val	CAG Gln 95	GAG Glu	2	88	
30	CGC	ACC	ATC Ile	TTC Phe 100	TTC Phe	AAG Lys	GAC Asp	GAC Asp	GGC Gly 105	AAC Asn	TAC	AAG Lys	ACC Thr	CGC Arg 110	GCC Ala	GAG Glu	3	36	
35	GTG Val	AAG Lys	TTC Phe 115	GAG Glu	GGC Gly	GAC Asp	ACC Thr	CTG Leu 120	Val	AAC Asn	CGC Arg	ATC	GAG Glu 125	CTG Leu	AAG Lys	GGC Gly	3	84	
35	ATC	GAC Asp 130	Phe	AAG Lys	GAG Glu	GAC Asp	GGC Gly 135	Asn	: ATC	: CTG : Leu	GGG Gly	CAC His	Lys	CTG Leu	GAG Glu	TAC	4	32	
40	AAC Asr 145	туг	AAC Asn	AGC Ser	CAC His	AAC Asn 150	Val	ТАТ	TATO	ATG Met	GCC Ala 155	Ası	AAC D Lys	G CAG	AAG Lys	AAC Asn 160	4	180	
45	GG(C ATO	AAC Lys	GTG Val	AAC Asr 165	Phe	Lys	ATC	C CGC	C CAC His	. Asr	TATO	C GAC	GAC 1 Asp	GGC Gly 175	AGC Ser		528	
50	GT(Va	G CAC	G CTO	GCC Ala 180	a Asp	C CAC	С ТАС 5 Туі	CAC Gli	G CAG	n Ası	C ACC	C CC	C ATO	e Gly	/ Asj	GGC Gly	• !	576	
	CC Pr	C GT(G CTO l Let 199	ı Leı	G CCC	C GAG	AA C	C CAC n Hi: 20	в Ту	C CTO	G AGO	C AC	C CA r Gl 20	n Se	C GCC	C CTG a Leu		624	
55	AG	C AA	A GA	c cc	C AA	C GAG	S AA	G CG	C GA	T CA	C AT	G GT	C CT	G CT	G GA	G TTC		672	246

	Ser	Lys 210	Asp	Pro	Asn	Glu	Lys 215	Arg	Asp	His	Met	Val 220	Leu	Leu	Glu	Phe	•	
5				GCC Ala													720	
10				TCT Ser													768	
				GTT Val 260													816	
15				AAG Lys													864	
20				GTG Val													912	
25				GAC Asp													960	
30				CCA Pro													1008	
				AGT Ser 340						Glu							1056	
35				Cys					Ile							AAG Lys	1104	
40			Arg	AAT Asn									Ala			AAG Lys	1152	
45		Glu					Glu					Met				ATT Ile 400	1200	
50						Met					Lys					GTG Val	1248	
					Glu					, Ala					Arg	CGT Arg	1296	
55	GGG	BAA B	AAA	AAA .	тст	' GGI	TGC	CTI	GTO	тто	TG#						1329 2	47

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Gly Lys Lys Ser Gly Cys Leu Val Leu
435 440
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5 (2) INFORMATION FOR SEQ ID NO:127:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 442 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 10 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 25 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 90 85 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 30 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 35 135 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 155 150 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 170 165 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 40 185 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 200 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 45 215 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 235 Gly Leu Arg Ser Arg Ala Gln Ala Ser Met Ala Ala Ile Arg Lys Lys 250 245 Leu Val Ile Val Gly Asp Gly Ala Cys Gly Lys Thr Cys Leu Leu Ile 50 265 Val Phe Ser Lys Asp Gln Phe Pro Glu Val Tyr Val Pro Thr Val Phe 280 Glu Asn Tyr Val Ala Asp Ile Glu Val Asp Gly Lys Gln Val Glu Leu 55 295 Ala Leu Trp Asp Thr Ala Gly Gln Glu Asp Tyr Asp Arg Leu Arg Pro

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	305	_		_	_	310		••- •	-1-		315	~	Dh.	0	-1 -	320			
	Leu	Ser	Tyr	Pro		Thr	Asp	vaı	тте		Met	Cys	Pue	ser		Asp			
				_	325					330	•	m	ml	D	335	1701			
_	Ser	Pro	Asp		Leu	GIu	Asn	11e		GIU	гàг	Trp	Thr		GIU	vaı			
5				340	_	_		_	345	-1.		**- 7	~ 1	350	T	T			
	Lys	His		Cys	Pro	Asn	vaı		TTE	TTE	ьeu	vaı		ASI	гуѕ	пλя			
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	Asp	Leu	Arg	Asn	Asp	GIU		Thr	Arg	Arg	GIU		Ala	цуѕ	Mer	гуу			
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10		Glu	Pro	vaı	гÀг		GIU	GIU	GIA	Arg	395	Mec	нта	ASII	AIG	400			
-	385	Ala	Dha	~1	Ma rec	390 Mot	Gl v	Circ	802	Λ1 -		ጥኮሎ	Lve	Δen	Glv				
	GIA	AIA	PIIE	GIY	405		GIU	Cys	SCI	410	כעם	* ***	נעם	nop	415				
	7~~	Glu	17-1	Dhe			בומ	Thr	Ara		Δla	1.e11	Gln	Δla		Ara			
15	Arg	GIU	vai	420	GIU	1100	ALU	****	425	71.14		200	·	430	5				
13	Glv	Lys	Lva		Ser	Glv	Cvs	Len		Leu									
	GIY	Бур	435	- 275	DC1	U	C , D	440.											
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			(2)	INE	FORM	TIO	I FOI	R SEC	O ID	NO:1	28:								
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25			(D)	TOP	DLOG	: 1:	inear	r											
		(:	ii) 1	MOLE	CULE	TYP	E: cl	DNA											
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30		•	(A) NAI	ME/KI		Codi	-	eque	nce									
30		•	(A (B) NAI	ME/KI	ON:	1:	1137	eque	nce									
30		•	(A (B) NAI	ME/KI	ON:		1137	equei	ıce									
30			(A (B (D) NAI) LOO) OTI	ME/KI CATION	ON: INFO	1:	1137 ION:	,										
			(A (B (D) NAI) LOO) OTI	ME/KI CATION	ON: INFO	1:	1137 ION:	,		NO:	128:		·				·	
30 35		(:	(A (B (D xi)) NAI) LOO) OTI SEQUI	ME/KI CATION HER I	ON: INFO	1: RMAT: CRIP'	1137 ION: TION	: SE	Q ID			N.T.C	CAG	CCA	GDD		48	
		(: GAC	(A (B (D xi)) NAI) LOO) OTI SEQUI	ME/KICATION HER SENCE	ON: INFO DES TCT	1: RMAT: CRIP' CAG	1137 ION: TION CAA	: SE	D ID	GAT	TAC						48	
	Met	(:	(A (B (D xi)) NAI) LOO) OTI SEQUI	ME/KICATION HER ENCE GAT Asp	ON: INFO DES TCT	1: RMAT: CRIP' CAG	1137 ION: TION CAA	: SE	Q ID AAC Asn	GAT	TAC			Pro			48	
		(: GAC	(A (B (D xi)) NAI) LOO) OTI SEQUI	ME/KICATION HER SENCE	ON: INFO DES TCT	1: RMAT: CRIP' CAG	1137 ION: TION CAA	: SE	D ID	GAT	TAC						48	
35	Met 1	;) GAC Asp	(A (B (D xi) CAT His) NAI) LOO) OTI SEQUI TAT Tyr	ME/KI CATIO HER : ENCE GAT Asp	DN: INFO DES TCT Ser	RMAT CRIP CAG Gln	1137 ION: TION CAA Gln	: SEC	Q ID AAC Asn 10	GAT Asp	TAC Tyr	Met	Gln	Pro 15	Glu			
	Met 1 GAG	GAC Asp	(A (B (D xi) CAT His) NAI) LOO) OTI SEQUITAT TYT	ME/KI CATIO HER : ENCE GAT Asp 5	DN: INFO DES TCT Ser	1 RMAT CRIP' CAG Gln	1137 ION: TION CAA Gln	: SEG ACC Thr	AAC Asn 10	GAT Asp	TAC Tyr	Met TGG	Gln GAG	Pro 15 AAG	Glu CAC		48	
35	Met 1 GAG	;) GAC Asp	(A (B (D xi) CAT His) NAI) LOO) OTI SEQUI TAT Tyr GAC Asp	ME/KI CATIO HER : ENCE GAT Asp 5	DN: INFO DES TCT Ser	1 RMAT CRIP' CAG Gln	1137 ION: TION CAA Gln	: SEC ACC Thr CTG Leu	AAC Asn 10	GAT Asp	TAC Tyr	Met TGG	Gln GAG Glu	Pro 15 AAG	Glu CAC			
35	Met 1 GAG	GAC Asp	(A (B (D xi) CAT His) NAI) LOO) OTI SEQUITAT TYT	ME/KI CATIO HER : ENCE GAT Asp 5	DN: INFO DES TCT Ser	1 RMAT CRIP' CAG Gln	1137 ION: TION CAA Gln	: SEG ACC Thr	AAC Asn 10	GAT Asp	TAC Tyr	Met TGG	Gln GAG	Pro 15 AAG	Glu CAC			
35	Met 1 GAG	GAC Asp GAC Asp	(A (B (D xi) CAT His TGG) NAI) LOO) OTI SEQUI TAT Tyr GAC Asp	ME/KI CATION HER : ENCE GAT Asp 5 CGG Arg	DN: DES TCT Ser GAC Asp	CRIP' CAG Gln CTG Leu	1137 ION: TION CAA Gln CTC Leu	: SEG ACC Thr CTG Leu 25	AAC Asn 10 GAC Asp	GAT Asp CCG Pro	TAC Tyr GCC Ala	Met TGG Trp	GAG Glu 30	Pro 15 AAG Lys	Glu CAG Glr	l		
35	Met 1 GAG Glu CAG	GAC Asp GAC Asp	(A (B (D xi) CAT His TGG Trp) NAI) LOO) OTI SEQUITAT TYT GAC ASP 20 ACA	ME/KICATIO	DN: INFO DES TCT Ser GAC Asp	CRIP' CAG Gln CTG Leu GCA	1137 ION: TION CAA Gln CTC Leu	: SEC ACC Thr CTG Leu 25	AAC Asn 10 GAC Asp	GAT Asp CCG Pro	TAC Tyr GCC Ala	TGG Trp	GAG Glu 30 CGG	Pro 15 AAG Lys	Glu CAG Gln		96	
35	Met 1 GAG Glu CAG	GAC Asp GAC Asp	(A (B (D xi) CAT His TGG Trp) NAI) LOO) OTI SEQUITAT TYT GAC ASP 20 ACA	ME/KICATIO	DN: INFO DES TCT Ser GAC Asp	CRIP' CAG Gln CTG Leu GCA	1137 ION: TION CAA Gln CTC Leu	: SEC ACC Thr CTG Leu 25	AAC Asn 10 GAC Asp	GAT Asp CCG Pro	TAC Tyr GCC Ala	TGG Trp	GAG Glu 30 CGG	Pro 15 AAG Lys	Glu CAG Gln		96	
35	Met 1 GAG Glu CAG	GAC Asp GAC Asp	(A (B (D xi) CAT His TGG Trp) NAI) LOO) OTI SEQUITAT TYT GAC ASP 20 ACA	ME/KICATIO	DN: INFO DES TCT Ser GAC Asp	CRIP' CAG Gln CTG Leu GCA	1137 ION: TION CAA Gln CTC Leu	: SEC ACC Thr CTG Leu 25	AAC Asn 10 GAC Asp	GAT Asp CCG Pro	TAC Tyr GCC Ala	TGG Trp	GAG Glu 30 CGG	Pro 15 AAG Lys	Glu CAG Gln		96	
35	Met 1 GAG Glu CAG	GAC Asp GAC Asp AGA	(A (B (D xi) CAT His TGG Trp AAG Lys 35) NAI) LOO) OTI SEQUI TAT Tyr GAC Asp 20 ACA	ME/KICATION HER GAT Asp 5 CGG Arg TTC Phe	DN: INFO DES TCT Ser GAC Asp	CRIP' CAG Gln CTG Leu GCA	1137 ION: TION CAA Gln CTC Leu TGG Trp 40	ACC Thr CTG Leu 25 TGT Cys	AAC Asn 10 GAC Asp AAC	GAT Asp CCG Pro	TAC Tyr GCC Ala CAC	TGG Trp CTC Leu 45	Gln GAG Glu 30 CGG Arg	Pro 15 AAG Lys AAG Lys	Glu CAG Gln GCG Ala		96	
35	Met 1 GAG Glu CAG Gln	GAC Asp GAC Asp AGA Arg	(A (B (D xi) CAT His TGG Trp AAG Lys 35	O NAME OF TAT TYPE	ME/KI CATIO HER ENCE GAT Asp 5 CGG Arg TTC Phe	DN: INFO DES TCT Ser GAC Asp ACG Thr	CRIP' CAG Gln CTG Leu GCA Ala	II37 ION: TION CAA Gln CTC Leu TGG Trp 40	: SEC ACC Thr CTG Leu 25 TGT Cys	AAC Asn 10 GAC Asp AAC Asn	GAT Asp CCG Pro TCC Ser	TAC Tyr GCC Ala CAC His	TGG Trp CTC Leu 45	Gln GAG Glu 30 CGG Arg	AAG Lys	Glu Gln Gln GCG Ala		96 144	
35 40 45	Met 1 GAG Glu CAG Gln	GAC Asp AGA Arg	(A (B (D xi) CAT His TGG Trp AAG Lys 35	O NAME OF TAT TYPE	ME/KI CATIO HER ENCE GAT Asp 5 CGG Arg TTC Phe	DN: INFO DES TCT Ser GAC Asp ACG Thr	CRIP' CAG Gln CTG Leu GCA Ala	II37 ION: TION CAA Gln CTC Leu TGG Trp 40	: SEC ACC Thr CTG Leu 25 TGT Cys	AAC Asn 10 GAC Asp AAC Asn	GAT Asp CCG Pro TCC Ser	TAC Tyr GCC Ala CAC His	TGG Trp CTC Leu 45	Gln GAG Glu 30 CGG Arg	AAG Lys	Glu Gln Gln GCG Ala		96 144	
35	Met 1 GAG Glu CAG Gln	GAC Asp GAC Asp AGA Arg	(A (B (D xi) CAT His TGG Trp AAG Lys 35	O NAME OF TAT TYPE	ME/KI CATIO HER ENCE GAT Asp 5 CGG Arg TTC Phe	DN: INFO DES TCT Ser GAC Asp ACG Thr	CRIP' CAG Gln CTG Leu GCA Ala	II37 ION: TION CAA Gln CTC Leu TGG Trp 40	: SEC ACC Thr CTG Leu 25 TGT Cys	AAC Asn 10 GAC Asp AAC Asn	GAT Asp CCG Pro TCC Ser	TAC Tyr GCC Ala CAC His	TGG Trp CTC Leu 45	Gln GAG Glu 30 CGG Arg	AAG Lys	Glu Gln Gln GCG Ala		96 144	
35 40 45	Met 1 GAG Glu CAG Gln GGG	GAC Asp AGA Arg	(A (B (D xi) CAT His TGG Trp AAG Lys 35 CAG	O NAI DOO DOO DOO DOO DOO DOO DOO DOO DOO DO	ME/KICATION CATION HER GAT Asp 5 CGG Arg TTC Phe GAG Glu	DN: INFO INFO DES TCT Ser GAC Asp ACG Thr	CRIP' CAG Gln CTG Leu GCA Ala ATC Ile 55	II37 ION: IION CAA Gln CTC Leu TGG Trp 40 GAA Glu	ACC Thr CTG Leu 25 TGT Cys	AAC Asn 10 GAC Asp AAC Asn GAC	GAT Asp CCG Pro TCC Ser	TAC Tyr GCC Ala CAC His	TGG Trp CTC Leu 45	Gln GAG Glu 30 CGG Arg	AAG Lys AAG Lys	Glu CAG Glr GCG Ala Lys		96 144	
35 40 45	Met 1 GAG Glu CAG Gln GGG Gly	GAC Asp AGA Arg ACA Thr	(A (B (D xi) CAT His TGG Trp AAG Lys 35 CAG Gln	O NAI O LOC O CTG	ME/KICATION CATION CATION CATION CAGGAGGIU	DN: INFO DES TCT Ser GAC Asp ACG Thr	CRIP' CAG Gln CTG Leu GCA Ala ATC Ile 55	TION: CAA Gln CTC Leu TGG Trp 40 GAA Glu	ACC Thr CTG Leu 25 TGT Cys GAG Glu	AAC Asn 10 GAC Asp AAC Asn GAC Asp	GAT Asp CCG Pro TCC Ser TTC Phe	TAC Tyr GCC Ala CAC His CGG Arg 60	TGG Trp CTC Leu 45 GAT Asp	Gln GAG Glu 30 CGG Arg	AAG Lys CTG Let	Glu CAG Gln GCG Ala Lys		96 144 192	
35 40 45	Met 1 GAG Glu CAG Gln GGG Gly	GAC Asp AGA Arg ACA Thr	(A (B (D xi) CAT His TGG Trp AAG Lys 35 CAG Gln	O NAI O LOC O CTG	ME/KICATION CATION CATION CATION CAGGAGGIU	DN: INFO DES TCT Ser GAC Asp ACG Thr	CRIP' CAG Gln CTG Leu GCA Ala ATC Ile 55	TION: CAA Gln CTC Leu TGG Trp 40 GAA Glu	ACC Thr CTG Leu 25 TGT Cys GAG Glu	AAC Asn 10 GAC Asp AAC Asn GAC Asp	GAT Asp CCG Pro TCC Ser TTC Phe	TAC Tyr GCC Ala CAC His CGG Arg 60	TGG Trp CTC Leu 45 GAT Asp	Gln GAG Glu 30 CGG Arg	AAG Lys CTG Let	Glu CAG Gln GCG Ala Lys		96 144 192	
35 40 45	GAG GIU CAG GIN GGG GIY CTC Leu	GAC Asp AGA Arg ACA Thr	(A (B (D xi) CAT His TGG Trp AAG Lys 35 CAG Gln	O NAI O LOC O CTG	ME/KICATION CATION CATION CATION CAGGAGGIU	DN: INFO DES TCT Ser GAC Asp ACG Thr AAC GAG Glu	CRIP' CAG Gln CTG Leu GCA Ala ATC Ile 55	TION: CAA Gln CTC Leu TGG Trp 40 GAA Glu	ACC Thr CTG Leu 25 TGT Cys GAG Glu	AAC Asn 10 GAC Asp AAC Asn GAC Asp	GAT Asp CCG Pro TCC Ser TTC Phe	TAC Tyr GCC Ala CAC His CGG Arg 60	TGG Trp CTC Leu 45 GAT Asp	Gln GAG Glu 30 CGG Arg	AAG Lys CTG Let	Glu CAG Gln GCG Ala Lys		96 144 192	
35 40 45	GAGGIU CAGGIN GGGGIY CTC Leu 65	GAC Asp AGA Arg ACA Thr	(A (B (D Xi) CAT His TGG Trp AAG Lys 35 CAG Gln	O NAI O LOO O TAT Tyr GAC Asp 20 ACA Thr ATC Ile	ME/KICATION CATION CATION CATON CATO	DN: INFO DES TCT Ser GAC Asp ACG Thr AAC Asn GAG Glu 70	CRIP' CAG Gln CTG Leu GCA Ala ATC Ile 55 GTC Val	TION: CAA Gln CTC Leu TGG Trp 40 GAA Glu ATC	ACC Thr CTG Leu 25 TGT Cys GAG Glu	AAC Asn 10 GAC Asp AAC Asn GAC Asn GAC	GAT Asp CCG Pro TCC Ser TTC Phe GAA Glu 75	TAC Tyr GCC Ala CAC His CGG Arg	TGG Trp CTC Leu 45 GAT Asp	Gln GAG Glu 30 CGG Arg GGC Gly	AAG Lys CTG Lev	Glu CAG Glr GCG Ala Lys CCG Pro 80		96 144 192	
35 40 45	GAGGIU CAGGIN GGGGIY CTC Leu 65	GAC Asp AGA Arg ACA Thr 50 Met	(A (B (D Xi) CAT His TGG Trp AAG Lys 35 CAG Gln	O NAI O LOO O TAT Tyr GAC Asp 20 ACA Thr ATC Ile	ME/KICATION CATION CATION CATON CATO	DN: INFO DES TCT Ser GAC Asp ACG Thr AAC Asn GAG Glu 70	CRIP' CAG Gln CTG Leu GCA Ala ATC Ile 55 GTC Val	TION: CAA Gln CTC Leu TGG Trp 40 GAA Glu ATC	ACC Thr CTG Leu 25 TGT Cys GAG Glu	AAC Asn 10 GAC Asp AAC Asn GAC Asn GAC	GAT Asp CCG Pro TCC Ser TTC Phe GAA Glu 75	TAC Tyr GCC Ala CAC His CGG Arg	TGG Trp CTC Leu 45 GAT Asp	Gln GAG Glu 30 CGG Arg GGC Gly	AAG Lys CTG Lev	Glu CAG Glr GCG Ala Lys CCG Pro 80		96 144 192 240	249

	Glu	Arg	Gly	Lys	Met 85	Arg	Val	His	Lys	Ile 90	Ser	Asn	Val	Asn	Lys 95	Ala		
5				ATA Ile 100													336	
10				GTG Val													384	
15				CTG Leu													432	
15				CTG Leu													480	
20				AAC Asn													528	
25			Thr	TAC Tyr 180												_ '	576	
30				GTG Val													624	
• .				TTC Phe													672	
35		Lys		GCC Ala													720	
40				GAC Asp													768	
45				CTG Leu 260											Phe		816	
50				AAC Asn										Tyr			864	
			Val	TAT Tyr									Gly				912	
55	AAC	TTC	AAG	ATC	CGC	CAC	AAC	ATC	GAG	GAC	GGC	AGC	GTG	CAG	CTC	GCC	960	250

										251							•
	Asn 305	Phe	Lys	Ile	Arg	His 310	Asn	Ile	Glu	Asp	Gly 315	Ser	Val	Gln	Leu	Ala 320	
5		CAC His															1008
10		GAC Asp									-						1056
45		GAG Glu															1104
15		ATC Ile 370										TAA					1140
20			(2)	INI	FORM	ATIO1	N FOI	R SEC) ID	NO:	129:						
25 .		(:	(A) (B) (C)	LENG TYPI STRA	E: at ANDE	379 mino ONESS	ACTEI amii acio 3: s: inea:	no ao i ingle	cids	٠						,	
30		(7	/) FI	RAGMI	ENT '	FYPE	E: p: : in	terna	al		NO.						
					Asp					Asn	NO:		Met	Gln		Glu	•
35	1 Glu	Asp	Trp	Asp 20	5 Arg	Asp	Leu	Leu	Leu 25	10 Asp	Pro	Ala	Trp	Glu 30	15 Lys	Gln	
		Arg	35			•		40	_				45				
40		50					55					60				Lys Pro	
	65					70				_	75					80 Ala	
45		_		-	85					90				Ile	95 Gly	Ala	
	Glu	Glu	Ile 115	100 Val	Asp	Gly	Asn	Val			Thr	Leu	Gly			Trp	
50	Thr	Ile 130		Leu	Arg	Arg	Asp 135	Pro		Val	Ala	Thr	Met		Ser	Lys	
	145	Glu				150	_				155					Asp 160	
55	-	-			165					170)				175		,
	Asp	AIG	THE	TAL	GIY	ьys	neu	1111	ברת	пλг	Pne	TTE	сув	1111	* ***	Gly	2

				180					185					190			
	Lys	Leu	Pro 195	Val	Pro	Trp	Pro	Thr 200	Leu	Val	Thr	Thr	Leu 205	Thr	Tyr	Gly	
5	Val	Gln 210	Суѕ	Phe	Ser	Arg	Tyr 215	Pro	Asp	His	Met	Lys 220	Gln	His	Asp	Phe	
	Phe 225	Lys	Ser	Ala	Met	Pro 230	Glu	Gly	Tyr	Val	Gln 235	Glu	Arg	Thr	Ile	Phe 240	
		Lys	Asp	qaA	Gly 245		Tyr	Lys	Thr	Arg 250	Ala	Glu	Val	Lys	Phe 255	Glu	
10	Gly	Asp	Thr	Leu 260		Asn	Arg	Ile	Glu 265		Lys	Gly	Ile	Asp 270		Lys	
	Glu	Asp	Gly 275		Ile	Leu	Gly	His 280		Leu	Glu	Tyr	Asn 285		Asn	Ser	
.=	His	Asn	_	Tyr	Ile	Met			Lys	Gln	Lys			Ile	Lys	Val	
15		290 Phe	Lys	Ile	Arg		295 Asn	Ile	Glu	Asp	_	300 Ser	Val	Gln	Leu		
	305 Asp	His	Tyr	Gln	Gln	310 Asn	Thr	Pro	Ile	Gly	315 Asp	Gly	Pro	Val	Leu	320 Leu	·
20	Pro	Asp	Asn	His	325 Tyr	Leu	Ser	Thr	Gln	330 Ser	Ala	Leu	Ser	Lys	335 Asp	Pro	
	Asn	Glu	Lys	340 Arg	Asp	His	Met	Val	345 Leu	Leu	Glu	Phę	Val	350 Thr	Ala	Ala	
		Ile	355	_	_			360					365				•
25	CI	370		,	,		375			-1-	- <i>x</i> -					•	
			(2)) INI	FORM	ATIO	N FOI	R SE	Q ID	NO:	130:						
20		(:				CHAR											
30			(B)	TYP	E: n	351 ucle	ic a	cid									
						DNES: Y: 1		_	е								
35		(:	ii) 1	MOLE	CULE	TYP	E: c	AMO									
		(:	ix) 1	FEAT	JRE:										٠		
						EY: (eque	nce						•	
40			(D) OTI	HER	INFO	RMAT	ION:									
		(:	xi) :	SEQU	ENCE	DES	CRIP'	TION	: SE	Q ID	NO:	130:					
45																CTG Leu	48
.0	1				5					10	,				15		
																GGC	96
50	val	GIU	neu	20	GIY	АБР	vai	ASII	25	urs	nys	PIIC	Ser	30	501	Gry	
		_														ATC	144
	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	. Lys	Leu	Thr	Leu 45	. Lys	Phe	Ile	
55	TGC	ACC	ACC	GGC	AAG	CTG	CCC	GTG	CCC	TGG	CCC	ACC	CTC	GTG	ACC	. ACC	192
																	252

	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr		
5	-												GAC Asp				240	
10													TAC Tyr				288	
4.5													ACC Thr				336	
15													GAG Glu 125				384	
20													AAG Lys				432	
25												Asp	AAG Lys				480	
30													GAG Glu				528	
0.5													ATC Ile			GGC Gly	576	
35									Tyr							CTG	624	•
40								Arg					Leu			TTC	672	
45		Thr					Thr					Glu				TCC Ser 240	720	
50						Ala					Glu					CCC Pro	768	
					Ala					Pro					Glr	A GAC A Asp	816	
55	GAG	CTT	' GAC	TTC	TCC	ATC	CTC	TTC	GAC	TAT	GAC	TAT	TTC	TAA 3	ccc	B AAC	864	253

	Glu	Leu	Asp 275	Phe	Ser	Ile	Leu	Phe 280	Asp	Tyr	Glu	Tyr	Leu 285	Asn	Pro	Asn		
5													CCC Pro		_		912	
10													CCA Pro				960	
45													GGA Gly	_			1008	
15													CCA Pro				1056	
20													CAC His 365				1104	
25													CTC Leu				1152	
30													TTC Phe				1200	
0.5													TTG Leu				1248	
35													TTC Phe				1296	
40													GAC Asp 445				1344	
45			Phe										AGA Arg				1392	
50												Ser	TGC				1440	
						Arg					Ser					GCC Ala	1488	
55	AAG	CGG	AGG	CAT	TCG	TGC	GCC	GAG	GCC	TTG	GTT	GCC	CTG	CCG	CCC	: GGA	1536	254

									,	200								
	Lys	Arg	Arg	His 500	Ser	Cys	Ala	Glu	Ala 505	Leu	Val	Ala	Leu	Pro 510	Pro	Gly		
5				CAG Gln													1584	
10				CAG Gln													1632	
15				GTG Val													1680	
				ATC Ile												TCG Ser	1728	
20				GCC Ala 580													1776	
25				GAG Glu								Gly					1824	
30				GAA Glu													1872	
35				GCC Ala													1920	
55				GAG Glu													1968	
40				GTG Val 660												ACA Thr	2016	
45				CGA Arg													2064	
50				CAT His									Gly			ATC Ile	2112	
EF		Ile										Pro				TAC Tyr 720	2160	
55	CAG	GTG	CAC	CGA	ATC	ACG	GGG	ААĀ	ACT	GTC	ACC	ACC	ACC	AGC	TAT	GAG	2208	255

	Gln	Val	His	Arg	Ile 725	Thr	Gly	Lys	Thr	Val 730	Thr	Thr	Thr	Ser	Tyr 735	Glu		
5				GGC Gly 740													2256	
10				AGG Arg												AGA Arg	2304	
15				ATT Ile													2352	
10				GTG Val													2400	
20				GTC Val													2448	
25				GCT Ala 820									Gln				2496	
30				GTC Val													2544	
				GAG Glu													2592	
35				TGG Trp													2640	: *
40				CTT Leu												Ile	2688	
45				GTA Val 900						Val					Arg	AAA Lys	2736	
50				Pro					Tyr					Ala		AAG Lys	2784	
			Pro					Asp					Cys			ACC Thr	2832	
55	CAT	GGA	GGC	CTG	GGG	AGC	CAG	CCT	TAC	TAC	ccc	CAG	CAC	. CCG	ATC	GTG	2880	256

																	•	
•	His 945	Gly	Gly	Leu	Gly	Ser 950	Gln	Pro	Tyr	Tyr	Pro 955	Gln	His	Pro	Met	Val 960	• .	,
5	GCC Ala																2928	
10			ACG Thr														2976	
45			GCC Ala 995				Gln					Leu					3024	
15	Leu		TAT Tyr			Pro					Ala						3072	
20			CAC His		Ser					Ala					Gln		3120	
25			CTG Leu	Leu					Thr					Ser			3168	
30			TAC Tyr		Pro			Gln					Gly				3216	
		Phe	CAG Gln 1075				Tyr					Ala					3264	
35	Arg		GGC Gly			Pro					Gln						3312	
40	TCC Ser 1105		CCC Pro		Val					Asn		Thr			Arg		3360	
45				Gly		Pro			Asp		Lys			Leu		GCG Ala	3408	
50			Thr		Lys					Leu			Thr		Leu	GAT Asp	3456	
EE		Val		Glu					Glu					Pro		AGA Arg	3504	
55	ААТ	CAG	ACG	TAA	•												3516 257	,

Asn Gln Thr 1170

55

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(2) INFORMATION FOR SEQ ID NO:131:
5
           (i) SEQUENCE CHARACTERISTICS:
             (A) LENGTH: 1171 amino acids
             (B) TYPE: amino acid
             (C) STRANDEDNESS: single
10
             (D) TOPOLOGY: linear
           (ii) MOLECULE TYPE: protein
           (v) FRAGMENT TYPE: internal
15
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:
     Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
                                          10
     Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20
                                      25
     Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
     Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
25
     Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
                          70
     Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                                          90
                      85
     Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
30
                                      105
     Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
                                  120
      Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
                                              140
35
                              135
      Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
                          150
                                              155
      Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                      165
                                          170
      Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
40
                                      185
      Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
                                                      205
                                  200
      Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
45
                              215
      Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
                          230
                                              235
      Gly Leu Arg Ser Arg Ala Met Asn Ala Pro Glu Arg Gln Pro Gln Pro
                      245
                                          250
      Asp Gly Gly Asp Ala Pro Gly His Glu Pro Gly Gly Ser Pro Gln Asp
50
                                      265
      Glu Leu Asp Phe Ser Ile Leu Phe Asp Tyr Glu Tyr Leu Asn Pro Asn
                                  280
      Glu Glu Pro Asn Ala His Lys Val Ala Ser Pro Pro Ser Gly Pro
```

295

Ala Tyr Pro Asp Asp Val Met Asp Tyr Gly Leu Lys Pro Tyr Ser Pro

	305				•	310					315					320
					325					330			Gly		335	
5	_		-	340					345			•	Pro	350		
•		-	355					360			•		His 365			
• .		370		_			375					380	Leu			
10	385					390					395		Phe			400
			_		405					410			Leu		415	
15				420					425				Phe	430		
			435					440					Asp 445			
		450					455					460	Arg			
20	465					470		•			475		Cys			480
					485					490			Ser		495	
25	_	_		500	•				505				Leu	510		
			515					520	•	•	•		Pro 525			
		530					535	*				540	Pro			
30	545					550			,		555		Ala			560
		_			565					570			Pro		575	
35			·	580					585				Arg	590		
			595					600					Glu 605			
		610				·	615					620				
40	625					630					635		Thr			640
					645					650			Ser		655	
45				660					665				His	670		
			675					680					Gly 685			
		690					695					700				
50	705					710					715		His			72
					725					730)		Thr		735	
55	Lys	Ile	· Val	Gly 740		Thr	. Lys		745	;			Lev	750)	
			9 # A-	7	. 77-	The second	. Tla			. ∧1-	. (2) .	, Tle	T.01	1.17C	. I.em	ΔΥ

			755					760					765			
	Asn	Ala 770	Asp	Ile	Glu	Leu	Arg 775	Lys	Gly	Glu	Thr	Asp 780	Ile	Gly	Arg	Lys
5	Asn 785	Thr	Arg	Val	Arg	Leu 790	Val	Phe	Arg	Val	His 795	Ile	Pro	Glu	Ser	Ser 800
	-	_			Ser 805	•				810					815	
				820	His				825					830		
10		-	835		Tyr	-	_	840					845	_		
		850			Ser	-	855					860				
15	865			_	Glu	870		,			875					880
					Phe 885					890					895	
00	_			900	Lys				905				_	910	-	
20			915		Gln		•	920					925			
		930			Asp Gly		935					940				
25	945		_		Ser	950					955			•		960
					965 Leu					970					975	
30				980	Leu				985			_		990		
			995		Gln	_		1000		_			1005			
		1010			Ser		1015		•		;	1020				
35	025					1030					1035					1040
					1045 Pro					1050					1055	
				1060					1065					1070		
40			1075		Ile			1080					1085			
		1090			Pro		1095					1100				
45	105	_				1110					1115	•				1120
					Pro 1125					1130					1135	
	дТĀ	val		1140	Lys	GIU	GIU		Asn 1145		дан	GIN	IIII	1150		. woh
50	Asp		Asn 1155		Ile	Ile	-	Lys 1160		Phe	Ser	Gly	Pro 1165		Ala	Arg
	Asn	Gln 1170	Thr										,			

55 (2) INFORMATION FOR SEQ ID NO:132:

5			(A) (B) (C)	LENG TYPE STRA	CE C TH: : nu NDED LOGY	3546 clei NESS	bas c ac : si	e pa id ngle	irs								
•			i) M x) F		ULE RE:	TYPE	: cD	NA				•		•			
10			(B)	roc	E/KE ATIO ER I	N: 1	3	543	quen	.ce							
15		(х	ai) S	EQUE	NCE	DESC	RIPT	: NOI	SEÇ	QI Q	NO:1	32:					
15		AAC Asn															48
20		CAC His															96
25		TTC Phe															144
30		AAG Lys 50															192
25		GAC Asp															240
35		CCC Pro															288
40		CTG Leu															336
45		GAG Glu															384
50		ATG Met 130															432
55												Pro				GGC Gly 160	480
55	TAC	CGC	GAG	CCG	CTT	TGC	TTG	AGC	ccc	GCT	AGC	AGC	GGC	TCC	TCT	GCC	528

•	Tyr	Arg	Glu	Pro	Leu 165	Сув	Leu	Ser	Pro	Ala 170	Ser	Ser	Gly	Ser	Ser 175	Ala		
•	AGC	TTC	ATT	TCT	GAC	ACC	TTC	TCC	CCC	TAC	ACC	TCG	CCC	TGC	GTC	TCG		576
5		Phe																
	CCC	TAA	AAC	GGC	GGG	CCC	GAC	GAC	CTG	TGT	CCG	CAG	TŤT	CAA	AAC	ATC	6	524
		Asn		_	_													
10			195					200					205					
		GCT															•	572
	PIO	210	nis	ıyı	SEI	PIU	215	TIII	ser	PIO	116	220	ser	PIO	Arg	Thr		
15																		
	AGC	CTC	GCC	GAG	GAC	AGC	TGC	CTG	GGC	CGC	CAC	TCG	CCC	GTG	CCC	CGT	•	720
	Ser	Leu	Ala	Glu	Asp	Ser	Cys	Leu	Gly	Arg	His	Ser	Pro	Val	Pro	Arg		
	225					230					235	•				240		
20	CCG	GCC	TCC	CGC	TCC	TCA	TCG	CCT	GGT	GCC	DAA	CGG	AGG	САТ	TCG	TGC		768
		Ala																
				_	245					250	_	_	_		255			
25		GAG															1	316
25	AIA	Glu	Ald	260	vai	AIA	теп	PIO	265	GIY	Ala	ser	PIO	270	Arg	sei		
				200					205					2.0				
	CGG	AGC	CCC	TCG	CCG	CAG	CCC	TCA	TCT	CAC	GTG	GCA	CCC	CAG	GAC	CAC	1	864
20	Arg	Ser		Ser	Pro	Gln	Pro		Ser	His	Val	Ala		Gln	Asp	His		
30			275	•				280					285					
	GGC	TCC	CCG	GCT	GGG	TAC	CCC	CCT	GTG	GCT	GGC	TCT	GCC	GTG	ATC	ATG	:	912
	Gly	Ser	Pro	Ala	Gly	Tyr	Pro	Pro	Val	Ala	Gly	Ser	Ala	Val	Ile	Met		
0.5		290					295					300						
35	CAT	GCC	CTC	אאר	אממ	CTC	acc	אככ	מאכ	TOO	CCT	ጥርጥ	ccc	እጥሮ	ccc	CCC		960
		Ala																900
	305					310					315	-7-	2			320		
40		ATG												•			1	800
	гÀв	Met	Trp	гув	325	ser	Pro	Asp	Pro	330	Pro	vaı	ser	Ala	335	Pro		
					323					330					333			
	TCC	AAG	GCC	GGC	CTG	CCT	CGC	CAC	ATC	TAC	CCG	GCC	GTG	GAG	TTC	CTG	1	056
45	Ser	Lys	Ala	Gly	Leu	Pro	Arg	His	Ile	Tyr	Pro	Ala	Val	Glu	Phe	Leu		
				340					345					350				
	GGG	CCC	ጥርር	GAG	CAG	GGC	GNG	A C C	מטמ	אאר	TCG	ርርጥ	CCA	CDD	TCC	ΔΤС	- 1	104
		Pro															_	101
50	• • 4		355	_ _		- 1		360	9				365			-		
														_	_	CCC	1	152
	ьeи	ьец 370	val	PTO	PIO	ınr	375	Pro	гуѕ	PTO	ьeи	Val 380	Pro	WIG	тте	Pro		
55		5,0					2,3					200						
	ATC	TGC	AGC	ATC	CCA	GTG	ACT	GCA	TCC	CTC	CCT	CCA	CTT	GAG	TGG	CCG	1	200

	Ile 385	Cys	Ser	Ile	Pro	Val 390	Thr	Ala	Ser	Leu	Pro 395	Pro	Leu	Glu	Trp	Pro 400		
5				CAG Gln													1248	
10			His	CAC His 420													1296	
45				CCA Pro													1344	
15				AAG Lys													1392	
20				CTT Leu											_	_	1440	
25				GTC Val													1488	
30				GAG Glu 500												_	1536	
				GCG Ala													1584	
35				GAG Glu										_			1632	
40	GTT Val 545															TTA Leu 560	1680	. •
45				TCT Ser												Glu	1728	
50										qaA					Tyr	GGC	1776	
•									Gln					Glu		Lys	1824	
55	GTT	GTG	TTT	ACT	GAG	AAG	ACC	ACA	GAT	GGA	CAG	CAA	ATT	'TGG	GAG	ATG	1872	263

	Val	Val 610	Phe	Thr	Glu	Lys	Thr 615	Thr	Asp	Gly	Gln	Gln 620	Ile	Trp	Glu	Met	
5					GAT Asp												1920
10					TAT Tyr 645											Val	1968
					ATC Ile											CAC His	2016
15					CCA Pro												2064
20					CTG Leu												2112
2 5					CCC Pro												2160
30		_			ATG Met 725												2208
35					CGC Arg												2256
	_				AGC Ser												2304
40					GCC Ala												2352
45					GGC Gly											•	2400
50					CAG Gln 805												2448
55					CGC Arg												2496
55	TAC	TGC	GAG	AAT	TTC	GCA	CCA	GGC	ACC	ACC	AGA	CCT	GGC	CCG	ccc	CCG	2544

																	*	
	Tyr	Cys	Glu 835	Asn	Phe	Ala	Pro	Gly 840	Thr	Thr	Arg	Pro	Gly 845	Pro	Pro	Pro	,	
5				GGT Gly												_	2592	
10				AAT Asn										_			2640	
45				CAA Gln													2688	
15				TTG Leu 900													2736	
20				TTT Phe											_		2784	
25				GTA Val												_	2832	
30		•		GAG Glu													2880	
or				GAC Asp													2928	
35				GCC Ala 980										_			2976	
40				CTG Leu			Pro					Val					3024	
45	Tyr		Val	CAG Gln		Phe					Asp		Met		_	CAC His	3072	
50		Phe			Ser	,	Met			Gly		Val				ACC Thr	3120	
				Lys		Asp					Thr					AAG Lys	3168	
55	TTC	GAG	GGC	GAC	ACC	ÇTG	GTG	AAC	CGC	ATC	GAG	CTO	AAG	GGC	: ATC	GAC	3216	265

	Phe	Glu	_	Asp 1060	Thr	Leu	Val		Arg 1065	Ile	Glu	Leu	-	Gly 1070	Ile	Asp	
5		AAG Lys					Ile					Leu					3264
10	Asn	AGC Ser 1090				Tyr					Lys						3312
15		GTG Val			Lys					Ile					Val		3360
		GCC Ala		His				_	Thr		_			Gly			3408
20 .		CTG Leu	Pro					Leu					Ala				3456
25		CCC Pro					Asp					Leu					3504
30	Ala	GCC Ala 1170				Leu					Leu			AAT			3546
			(2)) INI	FORM	ATIOI	N FOI	R SE	O ID	NO:	133:						
35		(;	(A) (B) (C)	EQUEI LENC TYPI STRA	ETH: E: ar ANDEI	118: mino ONES:	l am: acio S: s:	ino a 1 ingle	acid	S							·
40			li) N	TOPO MOLEO RAGMI	CULE	TYPI	E: p:	rote:									
45		()	ci) S	SEQUI	ENCE	DES	CRIP	rion	: SE	Q ID	NO:	133:		٠			
	1	Asn			5					10		_	_		15		
50		His		20					25					30			
50		Phe Lys	35			-		40					45				
		50 Asp					55		-			60					
55	65	Pro	_			70		-			75					80	

										201						
					85					90					95	
	Phe	Leu	Ser	Ala 100	Ala	Lys	Pro	Ala	Gly 105	Ala	Ser	Gly	Leu	Ser 110	Pro	Arg
5	Ile	Glu	Ile 115		Pro	Ser	His	Glu 120		Ile	Gln	Ala	Val 125		Pro	Leu
	Arg	Met 130	Arg	Asp	Ala	Gly	Leu 135	Leu	Val	Glu	Gln	Pro 140	Pro	Leu	Ala	Gly
•	Val 145	Ala	Ala	Ser	Pro	Arg	Phe	Thr	Leu	Pro	Val 155	Pro	Gly	Phe	Glu	Gly 160
10	Tyr	Arg	Glu	Pro	Leu 165	Сув	Leu	Ser	Pro	Ala 170	Ser	Ser	Gly	Ser	Ser 175	Ala
				180					185	-				190	Val	
15			195					200		_			205		Asn	
		210		=			215					220			Arg	
	225					230					235				Pro	240
20			•		245				_	250	-	_	_		Ser 255	_
				260					265	-				270	Arg	
25			275					280					285		Asp Ile	
		290					295					300			Pro	
30	305					310			-		315	-	_		Ala	320
	-		_	-	325			_		330					335 Phe	
				340					345	_			·	350	Ser	
35	_		355			_		360	_				365		Ile	
		370					375		-			380			Trp	
40	385					390					395					400 Pro
					405					410					415	Ala
	Val	Lys	Ala	420 Pro	Thr	Gly	Gly	His	425 Pro	Val	Val	Gln	Leu	430 His	Gly	Tyr
45	Met	Glu	435 Asn	Lys	Pro	Leu	Gly	440 Leu	Gln	Ile	Phe	Ile	445 Gly	Thr	Ala	Asp
	Glu	450 Arg	Ile	Leu	Lys	Pro	455 His	Ala	Phe	Tyr	Gln	460 Val	His	Arg	Ile	Thr
50	465 Gly	Lys	Thr	Val	Thr	470 Thr	Thr	Ser	Tyr	Glu	475 Lys	Ile	Val	Gly		480 Thr
	Lys	Val	Leu		485 Ile	Pro	Leu	Glu		490 Lys	Asn	Asn	Met		495 Ala	Thr
EE	Ile	Asp		500 Ala	Gly	Ile	Leu		505 Leu	Arg	Asn	Ala		510 Ile	Glu	Leu
55	Arg	Lys	515 Gly	Glu	Thr	Asp	Ile	520 Gly	Arg	Lys	Asn	Thr	525 Arg	Val	Arg	Leu

		530					535					540				
	Val		Arg	Val	His	Ile		Glu	Ser	Ser	Glv		Ile	Val	Ser	Leu
	545		•			550					555	J				560
	Gln	Thr	Ala	Ser	Asn	Pro	Ile	Glu	Cys	Ser	Gln	Arg	Ser	Ala	His	Glu
5					565				_	570		_			575	
	Leu	Pro	Met	Val	Glu	Arg	Gln	Asp	Thr	Asp	Ser	Cys	Leu	Val	Tyr	Gly
				580					585					590		
	Gly	Gln	Gln	Met	Ile	Leu	Thr,	Gly	Gln	Asn	Phe	Thr	Ser	Glu	Ser	Lys
			595					600					605			
10	Val		Phe	Thr	Glu	Lys		Thr	qsA	Gly	Gln		Ile	Trp	Glu	Met
		610	_,		_	_	615	_			<u>.</u>	620				
		Ala	Thr	vaı	Asp		Asp	ГÀЗ	Ser	GIn		Asn	Met	Leu	Phe	
	625	710	Dro	G2 11	Пз.г∽	630	7 ~ ~	7	T7	T1.	635	Mb	D	**- 7	· *	640
15	Giu	116	Pro	GIU	645	Arg	MDII	пув	nis	650	Arg	inr	PIO	Val	655	val
10	Asn	Phe	Tyr	Val		Asn	Glv	Lvs	Ara		Δra	Ser	Gln	Pro		His
			-1-	660			<u> </u>	27.5	665	Ly 5	A. 9	JCI	CIII	670	0111	*****
	Phe	Thr	Tyr		Pro	Val	Pro	Ala		Lvs	Thr	Glu	Pro		Asp	Glu
			675					680		•			685		•	
20	Tyr	Asp	Pro	Thr	Leu	Ile	Cys	Ser	Pro	Thr	His	Gly	Gly	Leu	Gly	Ser
		690					695					700				
	Gln	Pro	Tyr	Tyr	Pro	Gln	His	Pro	Met	Val	Ala	Glu	Ser	Pro	Ser	Cys
	705	_				710					715					720
	Leu	Val	Ala	Thr		Ala	Pro	Суѕ	Gln		Phe	Arg	Thr	Gly		Ser
25		n	•		725		~ 3 .			730	_		_ •		735	_
	ser	Pro	Asp		Arg	Tyr	GIn	GIn		Asn	Pro	Ala	Ala		Leu	Tyr
	Gln	Δτα	Ser	740	Car	T.e.v	Car	Dro	745	T 011	7 011	C111	Th. 22-	750	C15	Dro
	GIII	Arg	755	цуб	261	пеп	261	760	ser	ьеu	neu	GIY	765	GIII	GIII	PIO
30	Ala	Leu	Met	Ala	Ala	Pro	Leu		Leu	Ala	Asp	Δla		Ara	Ser	Val
		770					775					780		5		
	Leu	Val	His	Ala	Gly	Ser	Gln	Gly	Gln	Ser	Ser	Ala	Leu	Leu	His	Pro
	785					790					795					800
	Ser	Pro	Thr	Asn	Gln	Gln	Ala	Ser	Pro	Val	Ile	His	Tyr	Ser	Pro	Thr
35					805					810					815	
	Asn	Gln	Gln		Arg	Cys	Gly	Ser		Gln	Glu	Phe	Gln		Ile	Met
		~	~1	820	-1		_		825		_	_		830	_	_
	Tyr	Сув	Glu	Asn	Pne	Ala	Pro	_	Thr	Thr	Arg	Pro	-	Pro	Pro	Pro
40	1757	Car	835 Gln	C1**	C1 5	λ ~~	T 033	840	Desa	~ 1	0		845	mb	1707	T1.
40	VAI	850	GIII	GIY	GIII	Arg	855	ser	PIO	GIY	ser	860	PIO	IIII	vai	Ile
	Gln		Gln	Asn	Ala	Thr		Gln	Δτα	Δla	Δla		Asn	Glv	Pro	Pro
	865					870		0111	••••	7.14	875	- 7				880
		Ser	Asp	Gln	Lys		Val	Leu	Pro	Ala		Val	Thr	Ile	Lys	
45			_		885					890	•				895	
	Glu	Gln	Asn	Leu	Asp	Gln	Thr	Tyr	Leu	Asp	Asp	Val	Asn	Glu	Ile	Ile
				900					905					910		
	Arg	Lys	Glu	Phe	Ser	Gly	Pro	Pro	Ala	Arg	Asn	Gln	Thr	Arg	Ile	Leu
			915					920					925			
50	Gln		Thr	Val	Pro	Arg		Arg	Asp	Pro	Pro		Ala	Thr	Met	Val
	_	930	~ 3	a 3	~ .	_	935					940		_		
		ràs	GIÅ	GIU	GIU		Pne	Thr	GIA	val		Pro	He	Leu	val	Glu
	945	Aen	Glv	Δεν	Wa 1	950	G1++	u: ~	T ~	Dhe.	955	1707	e	G1	@1	960 Gly
55	neu	raħ	Gry	voħ	965	TOIL	GIA	UTR	пÀр	970	oer.	val	oct.	GIÀ	975	GIY
	Glu	Glv	Asp	Ala		Tvr	Glv	Lvs	Leu		Leu	Lvs	Phe	Ile		Thr
		4	-			-	- 2	<i>3</i> —								

			980					985					990				
	Thr Gly	Lys 995	Leu	Pro	Val		Trp .000	Pro	Thr	Leu		Thr .005		Leu	Thr		•
5	Tyr Gly 1010		Gln	Cys		Ser 1015	Arg	Tyr	Pro		His 020	Met	Lys	Gln	His		
	Asp Phe	Phe	Lys		Ala L030	Met	Pro	Glu		Tyr 035	Val	Gln	Glu		Thr .040	·	
	025 Ile Phe	Phe	Lys			Gly	Asn	Tyr			Arg	Ala		Val			
10	Phe Glu	Glv		1045 Thr	Leu	Val	Asn		.050 Ile	Glu	Leu	Lys		.055 Ile	Asp		
			1060				1	1065				1	070				
	Phe Lys	Glu 1075	_	GIY	Asn		Leu Loso	GIÀ	HIS	гàг		1085	туг	ASII	Tyr		
15	Asn Ser 1090		Asn	Val		Ile 1095	Met	Ala	Asp		Gln 100	Lys	Asn	Gly	Ile		
15	Lys Val		Phe		Ile		His	Asn		Glu		Gly	Ser				
	105 Leu Ala	asa	His		Gln	Gln	Asn	Thr		.115 Ile	Gly	Asp	Gly		l120 Val	٠	
00		_		1125				1	L130				1	135			
20	Leu Leu		1140	•			-	1145				1	150				
	Asp Pro	Asn 1155		Lys	Arg		His 1160	Met	Val	Leu		Glu 1165	Phe	Val	Thr		
	Ala Ala	Gly		Thr		Gly		Asp	Glu		Tyr						
25	1170					1175					1180						
		(2) INI	FORM	ATIOI	N FOI	R SE(Q ID	NO: I	134:							
	(i) S	EQUE	NCE (CHAR	ACTE	RIST:	ICS:									
30			LENO TYPI					airs									
			STR					e									
		(D)	TOP	OLOG	Y: 1:	inea	r										
35			MOLE		TYP	E: cl	DNA										
•	(1X)	FEAT	URE:													
) NAI				_	-	nce								
40		• •) OT														
	(xi)	SEQU	ENCE	DES	CRIP'	TION	: SE	Q ID	NO:	134:						
	ATG GTG			ccc	CAC	CAC	ama	TT C	n c c	aaa	стс	GTG	ccc	አጥ ሮ	СТС	4	. 8
45	Met Val															•	. •
	1			5					10					15			-
	GTC GAG															9	6
50	Val Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	GIY		
				~~m	000					OMC.	200		N N C	mm C	አጥሮ	14	14
	GAG GGC Glu Gly															1.5	. ·
55	_	35					40					45					
JJ	TGC ACC	ACC	GGC	AAG	CTG	ccc	GTG	ccc	TGG	CCC	ACC	CTC	GTG	ACC	ACC	19	92
															•		269

	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr		
5				GGC Gly													240	
10				TTC Phe													288	
15				TTC Phe 100													336	
				GAG Glu													384	
20				AAG Lys													432	
25				AGC Ser													480	•
30				GTG Val													528	I
35				GCC Ala 180													576	i
				CTG Leu													624	
40				CCC													672	
45				GCC Ala													720)
50	_			TCT Ser		_									_		768	3
55				GAG Glu 260													816	5
	GAC	GAG	CTG	GAG	CTG	GAG	TTG	GAT	CAG	AAG	GAC	GAA	CTG	ATC	CAG	AAG	864	270

	Asp	Glu	Leu 275	Glu	Leu	Glu	Leu	Asp 280	Gln	Lys	Asp	Glu	Leu 285	Ile	Gln	Lys	· .
5												ATC Ile 300			_		912
10												CAG Gln					960
45												GCC Ala			_	_	1008
15												AAG Lys			_		1056
20												GAC Asp					1104
25	Leu											TGT Cys 380					1152
30												GGA Gly					1200
35	CTG Leu											GTT Val					1248
55												TTT Phe					1296
40												AAG Lys					1344
45												CAA Gln 460					1392
50		Thr										Glu				AGC Ser 480	1440
55						Ser					Ile					GCT Ala	1488
JJ	GAT	GTC	CTT	GAA	GAG	ACC	CAC	TAT	' GAA	TAA	' GGA	GAA	TAT	TTA	' ATC	AGG	1536

. •	Asp	Val	Leu	Glu 500	Glu	Thr	His	Tyr	Glu 505	Asn	Gly	Glu	Tyr	Ile 510		Arg	
5		GGT Gly	_													_	1584
10		GTC Val 530															1632
		TTA Leu														GAA Glu 560	1680
15		GTG Val															1728
20		ATT Ile															1776
25		TCT Ser															1824
30		GAA Glu 610											•				1872
		GAT Asp															1920
35		AAA Lys															1968
40		CAC His			Asp										_		2016
45		ATC Ile															2064
50		TTT Phe 690														CTA Leu	2112
												Gly				GAT Asp 720	2160
55	TCT	ACA	ACC	AGA	TTT	TAC	ACA	GCA	TGT	GTG	GTA	GAA	GCT	TTT	GCC	TAT	2208

									•								
	Ser	Thr	Thr	Arg	Phe 725	Tyr	Thr	Ala	Cys	Val 730	Val	Glu	Ala	Phe	Ala 735	Tyr	
	CTG	CAT	TCC	AAA	GGA	ATC	ATT	TAC	AGG	GAC	CTC	AAG	CCA	GAA	AAT	CTC	2256
5	Leu	His	Ser	Lys 740	Gly	Ile	Ile	Tyr	Arg 745	Asp	Leu	Lys	Pro	Glu 750	Asn	Leu	
		CTA															2304
10	Ile	Leu	Asp 755	His	Arg	Gly	Tyr	Ala 760	Lys	Leu	Val	Asp	Phe 765	Gly	Phe	Ala	
		AAA															2352
	Lys	Lys 770	Ile	Gly	Phe	Gly	Lys 775	Lys	Thr	Trp	Thr	Phe 780	Cys	GIA	Thr	Pro	
15																	
		TAT Tyr															2400
	785	ıyı	vai	MIG	PIO	790	116	116	Беи	ABII	795	Gry	1110	VOD		800	
20		GAC															2448
	Ala	Asp	Tyr	Trp	Ser 805	Leu	Gly	Ile	Leu	Met 810	Tyr	Glu	Leu	Leu	Thr 815	Gly	
		CCA															2496
25	Ser	Pro	Pro	Phe 820		Gly	Pro	Asp	Pro 825	Met	Lys	Thr	Tyr	Asn 830	Ile	Ile	
		AGG															2544
30	Leu	Arg	Gly 835	Ile	Asp	Met	·Ile	Glu 840	Phe	Pro	Lys	Lys	11e 845	Ala	ГÀЗ	Asn	
																AGA	2592
	Ala	Ala 850	Asn	Leu	Ile	Lys	Lys 855	Leu	Cys	Arg	qaA	Asn 860	Pro	Ser	Glu	Arg	
35																	
		.GGG															2640
	ьеи 865	Gly	Asn	ьeu	ьуs	870	GIY	vai	гÀв	Asp	875	GIII	пув		пуs	880	·
40																CCT	2688
	Phe	Glu	Gly	Phe	Asn 885	Trp	Glu	GIY	Leu	Arg 890	Lys	GTA	Tnr	Leu	7nr 895	Pro	
																GAC	2736
45	Pro	Ile	Ile	Pro 900	Ser	Val	Ala	Ser	905		Asp	Thr	Ser	Asn 910		Asp	
•																GGA	2784
50	Ser	Phe	Pro 915		Asp	Asn	Asp	Glu 920		Pro	Pro	Asp	Asp 925		Ser	Gly	
		GAT															2802
	Trp	Asp 930		Asp	Phe												
		250								•							

274

(2) INFORMATION FOR SEQ ID NO:135:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 933 amino acids
- (B) TYPE: amino acid

5

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- 10 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

15	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu
				20		_			25		_			Val 30		_
	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
20	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
	Leu 65	Thr	Tyr	Gly	Val	Gln 70	Cys	Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys 80
25			_		85	•				90			-	Val	95	
				100					105					Arg 110		
			115		-	_		120			_		125	Leu	_	
30		130		_			135				_	140		Leu		
	145	_				150		-			155	-	-	Gln	_	160
35	_				165				_	170				Asp	175	
				180	_		-		185					Gly 190	_	
			195					200	_				205	Ser		
40		210					215	_	_			220		Leu		
	225					230					235			Tyr		240
45					245	_			_	250				Leu	255	
•				260	-				265	Ī		_	_	Ala 270		
	_		275					280		_	_		285	Ile		
50		290					295					300		Pro		
	305				-	310					315		_			Arg 320
55	Thr	Lys	Arg	Gln	Ala 325	Ile	Ser	Ala	Glu	Pro 330	Thr	Ala	Phe	Asp	11e 335	Gln
	Asp	Leu	Ser	His	Val	Thr	Leu	Pro	Phe	Tyr	Pro	Lys	Ser	Pro	Gln	Ser

				340					345					350		
	Lys	Asp	Leu 355		Lys	Glu	Ala	Ile 360		Asp	Asn	qaA	Phe 365	Met	Lys	Asn
5	Leu	Glu 370	Leu	Ser	Gln	Ile	Gln 375	Glu	Ile	Val	Asp	Cys 380	Met	Tyr	Pro	Val
	Glu 385	Tyr	Gly	Lys	Asp	Ser 390	Сув	Ile	Ile	Lys	Glu 395	Gly	Asp	Val	Gly	Ser 400
• .	Leu	Val	Tyr	Val	Met 405	Glu	Asp	Gly	Lys	Val 410	Glu	Val	Thr	Lys	Glu. 415	Gly
10				420					425					430	Leu	
•			435		- ·		_	440				_	445		Val	
15		450		_			455			_		460			Met	
	465		_			470				_	475				Lys	480
					485					490					Leu 495	
20				500			•	-	505	•	_			510	Ile Thr	
		_	515		-			520					525		Leu	
25		530					535					540			Gly	
	545					550					555				Cys	560
30	-		_		565				•	570					575 Asp	
			_	580	_				585					590	Tyr	
			595					600					605	•	Asn	
35		610					615					620			Val	
	625					630					635				Lys	640
40	Arg	His	Ile	Val	645 Asp	Thr	Arg	Gln	Gln	650 Glu		Ile	Arg	Ser	655 Glu	Lys
	Gln	Ile	Met	660 Gln	Gly	Ala	His		665 Asp	Phe	Ile	Val				Arg
	Thr	Phe	675 Lys	Asp	Ser	Lys		680 Leu	Tyr	Met	Leu		685 Glu		Cys	Leu
45	_	690 Gly	Glu	Leu	Trp		695 Ile	Leu	Arg	Asp		700 Gly	Ser	Phe	Glu	Asp
	705 Ser	Thr	Thr	Arg		710 Tyr	Thr	Ala	Cys			Glu	Ala	Phe		720 Tyr
50	Leu	His	ser	_	725 Gly	Ile	Ile	туr				Lys	Pro	Glu 750		Leu
	Ile	Leu	Asp 755	740 His	Arg	Gly	Tyr	Ala 760			Val	Asp	Phe	Gly		Ala
55	Lys	Lys 770		Gly	Phe	Gly	Lys 775	Lys		Trp	Thr	Phe 780	Суя		Thr	Pro
30	Glu		Val	Ala	Pro	Glu			Leu	Asn	Lys			Asp	Ile	Ser

	785					790					795					800	
	Ala	Asp	Tyr	Trp	Ser 805	Leu	Gly	Ile	Leu	Met 810	Tyr	Glu	Leu	Leu	Thr 815	Gly	
5	Ser	Pro	Pro	Phe 820	Ser	Gly	Pro	Asp	Pro 825	Met	Lys	Thr	Tyr	Asn 830	Ile	Ile	
	Leu	Arg	Gly 835	Ile	Asp	Met	Ile	Glu 840	Phe	Pro	Lys	Lys	Ile 845	Ala	Lys	Asn	
	Ala	Ala 850	Asn	Leu	Ile	Lys	Lys 855	Leu	Cys	Arg	Asp	Asn 860	Pro	Ser	Glu	Arg	
10	Leu 865	Gly	Asn	Leu	Lys	Asn 870	Gly	Val	Lys	Asp	Ile 875	Gln	Lys	His	Lys	Trp 880	
			Gly		885					890					895		
15			Ile	900					905					910			
			Pro 915		_	Asn	Asp	Glu 920	Pro	Pro	Pro	Asp	Asp 925	Asn	Ser	Gly	
	Trp	Asp 930	Ile	Asp	Phe		ż										
20			(2)	INI	FORM	OITA	N FO	R SE) ID	NO:	136:						
		(:	i) SI														
25			(B)	TYPI	Ξ: nι	2799 cle:	ic a	cid						•		٠.	
						ONES:		_	9						•		
		(:	ii) M	OLE	CULE	TYP	E: c	DNA									
30		- (:	ix) l	ורדי איבויה	TDE.												
			·														
	•		(A)	NAI	ME/KI	EY: (1	2795	equei	nce			,				
35			(A)	NAI	ME/KI		1	2795	equei	nce							
35			(A)	NAI LOC OTI	ME/KI CATIO HER :	ON: :	l RMAT	2795 ION:			NO:	136:	•				
35		(; GGC	(A) (B) (D) ki) S	NAI LOC OTI SEQUI	ME/KICATION HER INCE	ON: : INFO	1; RMAT CRIP TTA	2795 ION: TION CAG	: SE	Q ID GCG	CTC	CAG					48
35		(; GGC	(A) (B) (D)	NAI LOC OTI SEQUI	ME/KICATION HER INCE	ON: : INFO	1; RMAT CRIP TTA	2795 ION: TION CAG	: SE	Q ID GCG	CTC	CAG					48
	Met 1 GAG	GGC Gly CTG	(A) (B) (D) (ci) S ACC Thr	NAI LOO OTI SEQUI TTG Leu	ME/KICATION HER COGG Arg 5 CGG	ON: INFOI DESC GAT Asp	RMAT CRIP TTA Leu GCT	2795 ION: TION CAG Gln	: SEC TAC Tyr	Q ID GCG Ala 10 GAC	CTC Leu GAG	CAG Gln CTG	Glu GAG	Lys	Ile 15 GAG	Glu	48
40	Met 1 GAG	GGC Gly CTG	(A) (B) (D) (ci) S ACC Thr	NAI LOO OTI SEQUI TTG Leu	ME/KICATION HER COGG Arg 5 CGG	ON: INFOI DESC GAT Asp	RMAT CRIP TTA Leu GCT	2795 ION: TION CAG Gln	: SEC TAC Tyr	Q ID GCG Ala 10 GAC	CTC Leu GAG	CAG Gln CTG	Glu GAG	Lys	Ile 15 GAG	Glu	
	Met 1 GAG Glu GAT	GGC Gly CTG Leu	(A) (B) (D) (A) ACC Thr AGG Arg	TTG Leu CAG Gln 20	ME/KI CATIO HER : ENCE CGG Arg 5 CGG Arg	ON: INFOI DESC GAT Asp GAT Asp	CRIP TTA Leu GCT Ala	2795 ION: TION CAG Gln CTC Leu	TAC Tyr ATC Ile 25	GCG Ala 10 GAC Asp	CTC Leu GAG Glu	CAG Gln CTG Leu	GAG Glu GAG	CTG Leu 30	Ile 15 GAG Glu	TTG Leu AAG	
40	Met 1 GAG Glu GAT	GGC Gly CTG Leu	(A) (B) (D) (A) ACC Thr AGG Arg	TTG Leu CAG Gln 20	ME/KI CATIO HER : ENCE CGG Arg 5 CGG Arg	ON: INFOI DESC GAT Asp GAT Asp	CRIP TTA Leu GCT Ala	2795 ION: TION CAG Gln CTC Leu	TAC Tyr ATC Ile 25	GCG Ala 10 GAC Asp	CTC Leu GAG Glu	CAG Gln CTG Leu	GAG Glu GAG	CTG Leu 30	Ile 15 GAG Glu	Glu TTG Leu	96
40	Met 1 GAG Glu GAT Asp	GGC Gly CTG Leu CAG Gln	(A) (B) (D) (Ci) S ACC Thr AGG Arg AAG Lys 35	CAG Gln 20 GAC Asp	ME/KH CATIO HER : ENCE CGG Arg 5 CGG Arg GAA Glu	ON: INFOI DESC GAT Asp GAT Asp CTG Leu CGA	CRIP TTA Leu GCT Ala ATC Ile	2795 ION: TION CAG Gln CTC Leu CAG Gln 40	TAC Tyr ATC Ile 25 AAG Lys	Q ID GCG Ala 10 GAC Asp CTG Leu CAG	CTC Leu GAG Glu CAG Gln	CAG Gln CTG Leu AAC Asn	GAG Glu GAG Glu 45	CTG Leu 30 CTG Leu	GAC Asp	Glu TTG Leu AAG Lys	96
45	Met 1 GAG Glu GAT Asp	GGC Gly CTG Leu CAG Gln	(A) (B) (D) (Ci) S ACC Thr AGG Arg AAG Lys 35	CAG Gln 20 GAC Asp	ME/KH CATIO HER : ENCE CGG Arg 5 CGG Arg GAA Glu	ON: INFOI DESC GAT Asp GAT Asp CTG Leu CGA	CRIP TTA Leu GCT Ala ATC Ile	2795 ION: TION CAG Gln CTC Leu CAG Gln 40	TAC Tyr ATC Ile 25 AAG Lys	Q ID GCG Ala 10 GAC Asp CTG Leu CAG	CTC Leu GAG Glu CAG Gln	CAG Gln CTG Leu AAC Asn	GAG Glu GAG Glu 45	CTG Leu 30 CTG Leu	GAC Asp	Glu TTG Leu AAG Lys	96 144
40 45 50	Met 1 GAG Glu GAT Asp TAC Tyr	GGC Gly CTG Leu CAG Gln CGC Arg	(A) (B) (D) (Ai) S ACC Thr AGG Arg AAG Lys 35 TCG Ser	CAG Gln 20 GAC Asp	ME/KICATION HER ENCE CGG Arg CGG Arg GAA Glu ATC Ile CAG	ON: INFOI DESC GAT Asp GAT Asp CTG Leu CGA Arg	CRIP TTA Leu GCT Ala ATC Ile CCA Pro 55	2795 ION: TION CAG Gln CTC Leu CAG Gln 40 GCC Ala	TAC Tyr ATC Ile 25 AAG Lys ACC Thr	GCG Ala 10 GAC Asp CTG Leu CAG Gln	CTC Leu GAG Glu CAG Gln CAG	CAG Gln CTG Leu AAC Asn GCG Ala 60	GAG Glu GAG Glu 45 CAG Gln	CTG Leu 30 CTG Leu AAG Lys	GAG GAC ASP CAG GIn	TTG Leu AAG Lys AGC Ser	96 144
45	Met 1 GAG Glu GAT Asp TAC Tyr	GGC Gly CTG Leu CAG Gln CGC Arg	(A) (B) (D) (Ai) S ACC Thr AGG Arg AAG Lys 35 TCG Ser	CAG Gln 20 GAC Asp	ME/KICATION HER ENCE CGG Arg CGG Arg GAA Glu ATC Ile CAG	ON: INFOI DESC GAT Asp GAT Asp CTG Leu CGA Arg	CRIP TTA Leu GCT Ala ATC Ile CCA Pro 55	2795 ION: TION CAG Gln CTC Leu CAG Gln 40 GCC Ala	TAC Tyr ATC Ile 25 AAG Lys ACC Thr	GCG Ala 10 GAC Asp CTG Leu CAG Gln	CTC Leu GAG Glu CAG Gln CAG	CAG Gln CTG Leu AAC Asn GCG Ala 60	GAG Glu GAG Glu 45 CAG Gln	CTG Leu 30 CTG Leu AAG Lys	GAG GAC ASP CAG GIn	TTG Leu AAG Lys AGC Ser	96 144 192

	GCC	GAG	CCC	ACC	GCC	TTC	GAC	ATC	CAG	GAT	CTC	AGC	CAT	GTG	ACC	CTG	288
	Ala	Glu	Pro	Thr	Ala	Phe	Asp	Ile	Gln	Asp	Leu	Ser	His	Val	Thr	Leu	
					85					90					95		
5																	
-	CCC	TTC	TAC	CCC	AAG	AGC	CCA	CAG	TCC	AAG	GAT	CTT	ATA	AAG	GAA	GCT	336
	Pro	Phe	Tyr	Pro	Lys	Ser	Pro	Gln	Ser	Lys	Asp	Leu	Ile	Lys	Glu	Ala	
•				100					105					110			
						•											
10	ATC	CTT	GAC	AAT	GAC	TTT	ATG	AAG	AAC	TTG	GAG	CTG	TCG	CAG	ATC	CAG	384
	Ile	Leu	Asp	Asn	Asp	Phe	Met	Lys	Asn	Leu	Glu	Leu	Ser	Gln	Ile	Gln	
			115		•			120					125				,
		ATT															432
15	Glu	Ile	Val	Asp	Cys	Met	_	Pro	Val	Glu	Tyr		Lys	Asp	Ser	Cys	
		130					135					140					
		ATC		~ ~ ~	003	C2.C	C.T.C	000	TC N	ama	CTC	m v m	CTC.	አጥሮ	C A A	CAT	480
		Ile															400
20		TIE	гув	GIU	GIY	150	Vai	GTÅ	SEI	neu	155	ıyı	vaı	Mec	Giu	160	
20	145					130					133					100	
	CCT	AAG	GTT	AAĐ	GTT	ACA	ΔΔΔ	GAA	GGT	GTG	AAG	TTG	TGT	ACC	ATG	GGT	528
		Lys															
	 1	-7-			165					170			•		175	•	
25																	
	CCA	GGA	AAA	GTG	TTT	GGG	GAA	TTG	GCT	ATT	CTT	TAC	AAC	TGT	ACC	CGG	576
	Pro	Gly	Lys	Val	Phe	Gly	Glu	Leu	Ala	Ile	Leu	Tyr	Asn	Cys	Thr	Arg	
				180					185					190			
									•								
30		GCG												-	_		624
	Thr	Ala		Val	Lys	Thr	Leu		Asn	Val	Lys	Leu		Ala	TTE	Asp	
			195					200					205				
	003	CAA	mam	mmm	מאה	202	71 TO 71	አመረ	איזיכי	NCC	ת יים ת	CCA	CTC	አጥር '	מממ	CAT	672
35		Gln															0,2
33	Arg	210	Cys	PILE	GIN	1111	215	MEC	MEL	MIG	1111	220	пси	110	ay 5	1110	
		210					213										
	ACC	GAG	TAT	ATG	GAA	TTT	TTA	AAA	AGC	GTT	CCA	ACA	TTC	CAG	AGC	CTT	720
		Glu															
40	225		-			230		•			235					240	
	CCT	GAA	GAG	ATC	CTC	AGC	AAG	CTT	GCT	GAT	GTC	CTT	GAA	GAG	ACC	CAC	768
	Pro	Glu	Glu	Ile	Leu	Ser	Lys	Leu	Ala	Asp	Val	Leu	Glu	Glu	Thr	His	
	,				245					250					255		
45																	
		GAA															816
	Tyr	Glu	Asn		Glu	Tyr	Ile	Ile			Gly	Ala	Arg		Asp	Thr	
				260					265					270			
50	-		3 CC	3.55	200		001	3.00		7 x m	ama	3 AM	COM	ממט	G N C	TCD	864
50																TCA	004
	Pne	Phe		тте	ser	пÀŝ	GIĀ			ARU	val	THE	285		vaħ	Jer	•
			275					280					200				
	CCG	ልርጥ	αaĐ	GAC	CCA	GTC	ւեւսեւսեւ	Curu	מטע י	АСТ	<u> ተ</u> ሞል	GGA	ΑΔΑ	GGA	GAC	TGG	912
55																Trp	
		290		P			295					300		1	- 1-	•	

	•								
5	GGA Gly								960
	GCT Ala								1008
10	CAT His								1056
15	GCA Ala								1104
20	CTG Leu 370								1152
25	TTC Phe								1200
	TTT								1248
30	CAG Gln		•						1296
35	GAT Asp								1344
40	TAT Tyr 450								1392
45	AGG Arg								1440
	TGT Cys								1488
50	AGG Arg								1536
55	AAA Lys								1584

5													GCC Ala				1632
									-				TGG Trp				1680
10													TTC Phe				1728
15													ATT Ile				1776
20													TTA Leu 605				1824
25	Leu	Cys 610	Arg	Asp	Asn	Pro	Ser 615	Glu	Arg	Leu	Gly	Asn 620	TTG Leu	Lys	Asn	Gly	1872
	Val 625	Lys	Asp	Ile	Gln	Lys 630	His	Lys	Trp	Phe	Glu 635	Gly	TTT	Asn	Trp	Glu 640	1920
30	Gly	Leu	Arg	Lys	Gly 645	Thr	Leu	Thr	Pro	Pro 650	Ile	Ile	Pro	Ser	Val 655		1968
35	Ser	Pro	Thr	Asp 660	Thr	Ser	Asn	Phe	Asp 665	Ser	Phe	Pro	GAG Glu	Asp 670	Asn	Asp	2016
40	Glu	Pro	Pro 675	Pro	Asp	Asp	Asn	Ser 680	Gly	Trp	Asp	Ile	GAC Asp 685	Phe	Ser	Asp	2064
45	Pro	Pro 690	Val	Ala	Thr	Met	Val 695	Ser	.Lys	Gly	Glu	Glu 700	CTG Leu	Phe	Thr	Gly	2112
													AAC Asn				2160
50													TAC Tyr				2208
55										Lys					Trp	CCC Pro	2256

					ACC Thr												2304
5										*							
					AAG												2352
	Pro	Asp 770	His	Met	Lys	Gln	His 775	Asp	Phe	Phe	ГЛS	Ser 780	Ala	Met	Pro	Glu	
												020	a»a	000	7 7 C	ma C	2400
10					GAG Glu												2400
	785	ıyı	val	GIII		790	1111	116	FIIC	FIIC	795	nop	r.op	-		800	
·	` nna	እሮሮ	CGC	GCC	GAG	CTC	שממ	ጥጥር	GAG	GGC	GAC	ACC	CTG	GTG	AAC	CGC	2448
15					Glu												
	-,-		5		805		•			810	-				815		
	ATC	GAG	CTG	AAG	GGC	ATC	GAC	TTC	AAG	GAG	GAC	GGC	AAC	ATC	CTG	GGG	2496
					Gly												
20				820					825					830			
	CAC	AAG	CTG	GAG	TAC	AAC	TAC	AAC	AGC	CAC	AAC	GTC	TAT	ATC	ATG	GCC	2544
					Tyr												
			835					840					845				
25			ar a	220	AAC	000	3 000	220	CTC	7 7 C	THE C	אמ	አጥሮ	רפר	CAC	AAC	2592
					Asn												2372
	rpp	850	01		••••	-	855	-1-		•		860		_			
30	ATC	GAG	GAC	GGC	AGC	GTG	CAG	CTC	GCC	GAC	CAC	TAC	CAG	CAG	AAC	ACC	2640
					Ser												•
	865					870					875					880	
					GGC												2688
35	Pro	Ile	Gly	Asp	Gly	Pro	Val	Leu	Leu			Asn	His	Tyr			
					885					890					895		
	ACC	CAG	TCC	GCC	CTG	AGC	AAA	GAC	ccc	AAC	GAG	AAG	CGC	GAT	CAC	ATG	2736
	Thr	Gln	Ser		Leu						Glu	Lys	Arg			Met	
40				900					905					910			
	GTC	CTG	CTG	GAG	TTC	GTG	ACC	GCC	GCC	GGG	ATC	ACT	CTC	GGC	ATG	GAC	2784
	Val	Leu	Leu	Glu	Phe	Val	Thr	Ala	Ala	Gly	Ile	Thr	Leu	Gly	Met	qaA	
			915					920					925				
45	an a	OTT.C	מיזי כי		ረሞክ ክ												2799
		Leu			GTAA	•											7.5
	524	930	_	_, _													
50												-					
50			(2) IN	IFORM	ATIC	N FC	R SE	O II	NO:	137:	:					

(2) INFORMATION FOR SEQ ID NO:137:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 932 amino acids
 - (B) TYPE: amino acid

. 55

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

										,						
•	Met 1	Gly	Thr	Leu	Arg 5	Asp	Leu	Gln	Tyr	Ala 10	Leu	Gln	Glu	Lys	Ile 15	Glu
10	Glu	Leu	Arg	Gln 20	Arg	Asp	Ala	Leu	Ile 25	Asp	Glu	Leu	Glu	Leu 30	Glu	Leu
	-		35	-				40	_				45	Leu		
15	_	50					55					60		Lys		
	65					70			_		75			Ala		80
					85		_			90				Val	95	
20	•		_	100					105					Lys 110		
			115					120					125	Gln		
25		130		_			135				_	140	_	Asp		
	145		_		_	150		_			155			Met		160
	_	٦.			165					170				Thr	175	
30		-	_	180		_			185			•		Cys 190		
			195		_			200			_		205			
35	_	210					215					220		Ile		
	225		-			230		_			235			Gln		240
•					245				•	250				Glu	255	
40	•			260		-			265		_			Gly 270		
			275			_		280					285			Ser
45	•	290		_			295					300				Trp
	305					310					315					Val 320
-					325					330					335	Phe
50	-			340					345					350		Glu
	_		355					360					365			Ala
55		370	_				375			•		380				Gly
	Gly	Phe	Gly	Arg	Val	Glu	Leu	Val	Gln	Leu	Lys	Ser	Glu	Glu	Ser	Lys

	385					390					395					400
•	Thr	Phe	Ala	Met	Lys	Ile	Leu	Lys	Lys	Arg	His	Ile	Val	Asp	Thr	Arg
					405			•	•	410		•		-	415	
	Gln	Gln	Glu	His	Ile	Arg	Ser	Glu	Lys	Gln	Ile	Met	Gln	Gly	Ala	His
5				420		_			425					430		
	Ser	Asp	Phe	Ile	Val	Arg	Leu	Tyr	Arg	Thr	Phe	Lys	Asp	Ser	Lys	Tyr
			435			Ţ,		440	_			•	445		-	•
	Leu	Tyr	Met	Leu	Met	Glu	Ala	Сув	Leu	Gly	Gly	Glu	Leu	Trp	Thr	Ile
		450					455	-		•	-	460		-		
10	Leu	Arg	Asp	Arg	Gly	Ser	Phe	Glu	Asp	Ser	Thr	Thr	Arg	Phe	Tyr	Thr
	465	_	_	_	-	470			•		475				•	480
	Ala	Cys	Val	Val	Glu	Ala	Phe	Ala	Tyr	Leu	His	Ser	Lys	Gly	Ile	Ile
		-			485				_	490				_	495	
	Tyr	Arg	Asp	Leu	Lys	Pro	Glu	Asn	Leu	Ile	Leu	qaA	His	Arg	Gly	Tyr
15				500					505					510		
	Ala	Lys	Leu	Val	Asp	Phe	Gly	Phe	Ala	Lys	Lys	Ile	Gly	Phe	Gly	Lys
			515					520					525			
	Lys	Thr	Trp	Thr	Phe	Cys	Gly	Thr	Pro	Glu	Tyr	Val	Ala	Pro	Glu	Ile
		530					535		,			540			•	
20	Ile	Leu	Asn	Lys	Gly	His	Asp	Ile	Ser	Ala	Asp	Tyr	Trp	Ser	Leu	Gly
	545					550					555					560
	Ile	Leu	Met	Tyr	Glu	Leu	Leu	Thr	Gly	Ser	Pro	Pro	Phe	Ser	Gly	Pro
					565					570					575	•
	Asp	Pro	Met	Lys	Thr	Tyr	Asn	Ile	Ile	Leu	Arg	Gly	Ile	Asp	Met	Ile
25				580					585					590		
	Glu	Phe	Pro	Lys	Lys	Ile	Ala	Lys	Asn	Ala	Ala	Asn	Leu	·Ile	Lys	Lys
			595				•	600					605			
	Leu	-	Arg	Asp	Asn	Pro			Arg	Leu	Gly		Leu	Lys	Asn	Gly
		610					615	-				620				_
30		Lys	Asp	Ile	Gln		His	Lys	Trp	Phe		Gly	Phe	Asn	Trp	
	625	_	_	_		630	_			_	635	<u>.</u>	_	_		640
	GIY	Leu	Arg	гÀг	_	Thr	Leu	Thr	Pro		TTE	ше	Pro	Ser		Ala
	_	D	m1	7	645	0		5 1		650	D1	D	a 1	3	655	2
25	ser	Pro	Thr	_	Thr	ser	ASI	Pne	_	ser	Pne	PIO	GIU	Asp	ASI	Asp
35	~1	D	D	660	3	3	3	a	665		3	~ 1_	7	670	C	2
	GIU	Pro		Pro	Asp	Asp	Asn		GIY	Trp	Asp	TTE	-	Phe	ser	Asp
	Dana	D	675	71.	(Tille se	M	1703	680	T	01	a 1	~ 1	685	Dho	mb.~	C11
	PIO		vaı	Ala	IIII	Mec	695	ser	тув	СТУ	GIU	700	Leu	Phe	1111	GIY
40	Wa l	690	Dro	Tla	Lon	17-1		T 011	7 cm	Clv	N an		700	Gly	Uic	Lys
70	705	VAI	FIO	116	цец	710	GIU.	Deu	Asp	Gry	715	Val	VPII	GIY	1110	720
		Ser	Va 1	Ser	Gly		Glv	Glu	Glv	Aen		Thr	ጥህንግ	Glv	Lve	Leu
	FIIC	Der	val	SCI	725	GIU	CLY	Giu	Gly	730	AIU	1111	- 7 -	Ory	735	DCu
	Thr	T.011	Lave	Dhe		Cve	Thr	ጥኮሎ	Glv		I.e.11	Dro	Val	Pro		Pro
45	1111	пси	Lys	740	110	Cys	* 111	1111	745	пув	пси		vai	750	115	,110
40	Thr	Len	٧a٦		Thr	T.en	ጥክャ	ጥህን		Val	Gln	Cvs	Phe	Ser	Ara	Tvr
	1111	Deu	755	****	****	200	****	760	017	V 4 1	0111	C J D	765	501		-1-
	Pro	λαη		Met	Lvg	Gln	Hie		Dhe	Dhe	Lve	Ser		Met	Pro	Glu
		770			-	Q111	775	ASP	1110	1110	БуБ	780	nu			014
50	Glv		Val	Gln	Glu	Ara		Tle	Phe	Phe	Tive		Agn	Glv	Asn	Tyr
50	785	-1-			u	790	- ***	-16			795		p	 y	1	800
		Thr	Ara	Ala	Glu		Ive	Phe	Glu	Glv		Thr	Len	Val	Agn	Arg
	-y 3		9		805	- 41	_, 5		u	810	· rop				815	5
	Ile	Glu	Leu	Lvs		Ile	Asp	Phe	Lvs		Asp	Glv	Asn	Ile		Gly
55				820	1				825			1		830		1
	His	Lvs	Leu		Tvr	Asn	Tvr	Asp		His	Asn	Val	Tvr			Ala
		J			- .		-1-						-1-			

	Asp	Lys	835 Gln	Lys	Asn	Gly	Ile	840 Lys	Val	Asn	Phe	Lys	845 Ile	Arg	His	Asn		
	Tle	850 Glu	Asn	Glv	Ser	Val	855 Gln	Leu	Ala	Asn	His	860 Tvr	Gln	Gln	Asn	Thr		
5	865			U -1		870	·		••••		875		· · · ·			880		
		Ile	Gly	Asp	Gly 885		Val	Leu	Leu	Pro		Asn	His	Tyr	Leu 895			
	Thr	Gln	Ser	Ala 900		Ser	Lys	Asp	Pro 905		Glu	Lys	Arg	Asp 910		Met		
10	Val	Leu	Leu 915		Phe	Val	Thr	Ala 920		Gly	Ile	Thr	Leu 925		Met	Asp		
	Glu	Leu 930	-	Lys														
15			(2)	INI	FORM	TION	FOF	R SEÇ	Q ID	NO:	38:							
20		i)	(A) (B) (C)	EQUENCE TYPE STRA	ETH: E: nu ANDEI	2184 iclei ONESS	basic ac	se pa cid ingle	airs									
25			ix) I	OLEC	JRE:													
30		(5	(B)	NAN LOC OTI	CATIO	ON: 1	RMAT	2181 ION:	_		NO.							
30		()	(1) :	SEQUI	ENCE	DESC	JRIP.	rion :	: SE(מז נ	NO:	138:						
0.5		GTG Val															. 48	
35		GAG															96	
	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly		
40		GGC Gly															144	
			35					40					45					
45		ACC Thr															192	
	-7-	50		-			55			-		60						
		ACC Thr												_			240	
50	65					70				4	75					80		
		CAC His												_	_	_	288	
55			_		85	-				90					95			
	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	GCC	GAG	336	283

	Arg	Thr	Ile	Phe 100	Phe	Lys	qaA	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Gļu	
5		AAG Lys												Leu			384
10		GAC Asp 130															432
_		TAC Tyr															480
15		ATC Ile															528
20		CAG Gln															576
25		GTG Val															624
30		AAA Lys 210															672
		ACC Thr															720
35		CTC Leu												Val			768
40		TGG Trp															816
45		TTC Phe										4					864
50		CAG Gln 290															912
		CAG Gln															960
55	ATC	ATC	CGC	TGC	CTG	CAG	TGG	ACC	ACT	GTC	ATC	GAA	CGC	ACC	TTC	CAT	1008

	Ile	Ile	Arg	Сув	Leu 325	Gln	Trp	Thr	Thr	Val 330	Ile	Glu	Arg	Thr	Phe 335	His		
5								GAG Glu									1056	
10				GGC				CAG Gln 360									1104	
	TCG Ser	GGC Gly 370	TCA	CCC Pro	AGT Ser	GAC Asp	AAC Asn 375	TCA Ser	GGG Gly	GCT Ala	GAA Glu	GAG Glu 380	ATG Met	GAG Glu	GTG Val	TCC Ser	1152	
15	Leu	GCC					CGC	GTG Val									1200	•
20					Lys	GGC		TTC Phe			GTG						1248	
25				Gly	Arg			GCC Ala	Met	AAG				Lys	GAA		1296	
					GAC			GCC Ala									1344	
30	CTG Leu	CAG Gln	435 AAC Asn	TCC Ser	AGG Arg	CAC His	CCC Pro	TTC Phe	CTC Leu	ACA Thr	GCC Ala	CTG Leu	AAG Lys	TAC Tyr	TCT Ser	TTC Phe	1392	
35	CAG	450 ACC	CAC	GAC	CGC	CTC	455 TGC	TTT	GTC	ATG	GAG	460	GCC	AAC	GGG	GGC	1440	
40	465 GAG	CTG	TTC	TTC	CAC	470	TCC	CGG	GAA	CGT	475 GTG	TTC	TCC	GAG	GAC	480 CGG	1488	
	Glu				485					490			•		495		1536	
45	Ala	Arg	Phe	Tyr 500	Gly	Ala	Glu	Ile	Val 505	Ser	· Ala	Leu	ı Asp	Tyr 510	Leu	His	1584	
50	Ser	Glu	Lys 515	Asn	Val	. Val	. Tyr	520	Asp	Lev	Lys	Let	1 Glu 525	Asr	Let	ATG Met	1304	-
EE			Lys					Lys					e Gly			C AAG E Lys	1632	
55	GAG	GGG	ATC	: AAG	GAC	GG7	r GCC	C ACC	TA C	OAA, E	ACC	C TT	r TG0	C GG(C AC	A CCT		285

	Glu 545	Gly	Ile	Lys	Asp	Gly 550	Ala	Thr	Met	Lys	Thr 555	Phe	Cys	Gly	Thr	Pro 560	
5						GAG Glu											1728
10						CTG Leu											1776
						AAC Asn										ATC Ile	1824
15						CGC Arg									_		1872
20						CTG Leu 630										_	1920
25						GCC Ala											1968
30						CAC His											2016
35						TCG Ser										_	2064
55			_			ATC Ile											2112
40						AGC Ser 710											2160
45						ACG Thr		TGA				·		•			2184
50						ATIO				NO:	139:						
	·	(:	(A) (B)	LEN	GTH: E: a	CHAR 727 mino DNES	ami:	no a d	cids						•	·	
55			(D)	TOP	OLOG	Y: 1	inea	r									

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

E		()	ki) 5	EQUE	ENCE	DESC	RIPT	CION:	SEÇ	QID	NO: 1	139:				
5	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile 15	Leu
	_	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
10	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
·	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
15	65		_			70					75			His		80
				•	85					90				Val	95	
00	_			100		_	_	_	105		_			Arg 110		
20		•	115		-	_		120					125	Leu Leu		
		130					135					140		Gln		
25	145	_				150		_			155			Asp		160
	_		•		165		_		_	170				Gly	175	
30				180	-		-		185					190 Ser		
	Ser	Lys	195 Asp	Pro	Asn	Glu	Lys	200 Arg	Asp	His	Met	Val	205 Leu	Leu	Glu	Phe
		210 Thr	Ala	Ala	Gly	Ile	215 Thr	Leu	Gly	Met		220 Glu	Leu	Tyr	Lys	
35	225 Gly	Leu	Arg	Ser		230 Gly	Thr	Met	Ser		235 Val	Ala	Ile	Val		240 Glu
	Gly	Trp	Leu	His 260		Arg	Gly	Glu	Tyr 265		Lys	Thr	Trp	Arg 270	255 Pro	Arg
40	Tyr	Phe	Leu 275			Asn	Asp	Gly 280			Ile	Gly	Tyr 285	Lys	Glu	Arg
	Pro	Gln 290	Asp	Val	Asp	Gln	Arg 295	Glu	Ala	Pro	Leu	Asn 300	Asn	Phe	Ser	Val
45	305					310	_				315			Asn		320
					325					330				Thr	335	
				340					345					Ile 350		
50			355					360					365			
		370					375					380	ı	Glu		
55	385		Lys	27.0	ьys	390		val		rie C	395			Glu		400

Lys Leu Leu Gly Lys Gly Thr Phe Gly Lys Val Ile Leu Val Lys Glu

					405					410					415	
-	Lys	Ala	Thr	Gly 420	Arg	Tyr	Tyr	Ala	Met 425	Lys	Ile	Leu	Lys	Lys 430	Glu	Val
-	Ile	Val			Asp	Glu	Val		His	Thr	Leu	Thr	Glu 445	Asn	Arg	Val
5	_	~ 1	435		3	774 _	D	440	7	mb se	71.	T 011		T1	C02	Dhe
		450					455					460		Tyr		
	Gln	Thr	His	Asp	Arg	Leu	Cys	Phe	Val	Met		Tyr	Ala	Asn	Gly	
	465					470					475					480
10	Glu	Leu	Phe	Phe	His 485	Leu	Ser	Arg	Glu	Arg 490	Val	Phe	Ser	Glu	Asp 495	
	Ala	Arg	Phe	Tyr 500	Gly	Ala	Glu	Ile	Val 505	Ser	Ala	Leu	qaA	Tyr 510	Leu	His
15	Ser	Glu	Lys 515	Asn	Val	Val	Tyr	Arg 520	Asp	Leu	Lys	Leu	Glu 525	Asn	Leu	Met
	Leu	asp		Asp	Glv	His	Ile		Ile	Thr	Asp	Phe	Gly	Leu	Cys	Lys
		530	-1-		,2		535				•	540	•		•	•
	Glu	Gly	Ile	Lys	qaA	Gly	Ala	Thr	Met	Lys	Thr	Phe	Cys	Gly	Thr	Pro
	545	•		•	-	550				-	555				•	560
20	Glu	Tyr	Leu	Ala	Pro 565	Glu	Val	Leu	Glu	Asp 570	Asn	Asp	Tyr	Gly	Arg 575	Ala
	Val	Asp	Trp	Trp 580		Leu	Gly	Val	Val 585	Met	Tyr	Glu	Met	Met 590	Cys	Gly
	Ara	T.en	Pro			Asn	Gln	Asn		Glu	Lvs	Leu	Phe	Glu	Leu	Ile
25	·		595					600					605			
		610					615					620		Glu		
	Ser 625	Leu	Leu	Ser	Gly	Leu 630	Leu	Lys	rys	Asp	Pro 635	Lys	Gln	Arg	Leu	Gly 640
30	Gly	Gly	Ser	Glu	Asp 645	Ala	Lys	Glu	Ile	Met 650	Gln	His	Arg	Phe	Phe 655	Ala
	Gly	Ile	Val	Trp		His	Val	Tyr	Glu 665		Lys	Leu	Ser	Pro 670		Phe
25	Lys	Pro	Gln 675			Ser	Glu	Thr	Asp		Arg	Tyr	Phe 685	Asp		Glu
35	Phe		Ala	Gln	Met	Ile	Thr 695	Ile		Pro	Pro	Asp	Gln		Asp	Ser
	Mot	690		V=1) en	Sar			λνα	Dro	Hie			Gln	Phe	Ser
	705		Cys	AGT	vsħ	710		vrA	A. Y	FIU	715		110	0111		720
40	Tyr	Ser	Ala	Ser	Ser 725		Ala									
			(2) IN	FORM	ATIO	N FO	R SE	Q ID	NO:	140:					

45 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2394 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

50

- (A) NAME/KEY: Coding Sequence
- (B) LOCATION: 1...2391
 - (D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

				_					_	-								
5				CTG Leu													48	D
10				TAT Tyr 20													96	
15				TAC Tyr													144	
10				ACA Thr													192	
20				GGA Gly													240	
25				CGG Arg													288	
30				TAT Tyr 100													336	
35				CTG Leu											_	_	3.84	
				CAG Gln											_		432	
40				CAG Gln													480	
45				ACA Thr													528	
50				CCT Pro 180													576	
55				ATC Ile										Сув			624	
	GGG	GAT	GAG	ATC	TTC	CTA	CTG	TGT	GAC	AAG	GTG	CAG	AAA	GAG	GAC	ATT	672	289

	Gly	Asp 210	Glu	Ile	Phe	Leu	Leu 215	Cys	Asp	Lys	Val	Gln 220	Lys	Glu	Asp	Ile		
5														TCC Ser			720	
10				Val										ACC Thr			768	
														ATG Met 270		CTG Leu	816	
15														TTC Phe			864	
20														CGT Arg			912	
25														TTC Phe			960	
30														CCT Pro			1008	
														CCC Pro 350			1056	
35 .														ATG Met			1104	
40			Gly					Ala					Pro	GCC Ala			1152	
45		Val					Pro					Ala				GTA Val 400	1200	
50						Ala					Pro					GGC	1248	
					Val					Pro					Ala	GGG	1296	
55	GAA	. GGA	ACG	CTG	TCA	GAG	GCC	CTG	CTC	CAG	CTG	CAC	TT1	GAT	GAT	GAA.	1344	290

	Glu	Gly	Thr 435	Leu	Ser	Glu	Ala	Leu 440	Leu	Gln	Leu	Gln	Phe 445	Asp	Asp	Glu		
5													GCT Ala				1392	
10		-											CTG Leu				1440	
45													CTG Leu				1488	
15													AGG Arg				1536	
20													AAT Asn 525				. 1584	
25													GAC Asp				1632	
30													GCC Ala				1680	
													ATC Ile				1,728	
35													TCC Ser				1776	
40													TTC Phe 605				1824	
45													ACC Thr				1872	
50												His	ATG Met				1920	
											Tyr					ACC	1968	
55	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	: GCC	GAG	GTG	AAG	2016	291

									•	LUL							
	Ile	Phe	Phe	Lys 660	Asp	Asp	Gly	Asn	Tyr 665	Lys	Thr	Arg	Ala	Glu 670		Γλε	
5				GAC Asp										Gly			2064
10				GAC Asp													2112
				AAC Asn													2160
15				TTC Phe													2208
20				CAC His													2256
25				GAC Asp												AAA Lys	2304
30				GAG Glu													2352
				ATC Ile													2394
35			(2) IN	FORM	ATIO:	n fo	R SE	Q ID	NO:	141:						
40		((A) (B) (C)	EQUE LEN TYP STR TOP	GTH: E: a ANDE	797 mino DNES	ami aci S: s	no a d ingl	cids				.•			,	
45				MOLE RAGM			_										
		(xi)	SEQU	ENCE	DES	CRIP	TION	: SE	Q ID	NO:	141:					
50	1				5					10					15		
				20					25					30		Met Gly	•
55			35					40					45			e Asn	29

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		50					55					60				
	Gly 65	Tyr	Thr	Gly	Pro	Gly 70	Thr	Val	Arg	Ile	Ser 75	Leu	Val	Thr	Lys	qaA 08
5				_	85					90			Lys	_	95	
	•	_		100					105				Cys	110		
			115		_			120					Asp 125			
10		130			_		135					140	Phe			
	145					150					155		Val			160
15					165					170			Leu		175	
				180					185				Pro Ser	190		
20			195					200					205 Lys			
20		210			•		215	_	_	-		220	Gly			
	225		-			230		_	_		235		Arg	-		240
25			-		245	_				250			Ser		255	
	-		_	260					265				Glu	270		
30			275					280					285 Lys			
	Thr	290 Tyr	Glu	Thr	Phe	Lys	295 Ser	Ile	Met	Lys	Lys	300 Ser	Pro	Phe	ser	Gly
	305 Pro	Thr	Asp	Pro	Arg	310 Pro	Pro	Pro	Arg	Arg	315 Ile	Ala	Val	Pro		320 Arg
35	Ser	Ser	Ala		325 Val	Pro	Lys	Pro		330 Pro	Gln	Pro	туr		335 Phe	Thr
	Ser	Ser		340 Ser	Thr	Ile	Asn		345 Asp	Glu	Phe	Pro	Thr	350 Met	Val	Phe
40	Pro	Ser	355 Gly	Gln	Ile	Ser	Gln 375		Ser	Ala	Leu	Ala 380	365 Pro	Ala	Pro	Pro
	Gln 385	-	Leu	Pro	Gln	Ala 390			Pro	Ala	Pro	_	Pro	Ala	Met	Val
45		Ala	Leu	Ala	Gln 405	Ala	Pro	Ala	Pro	Val 410		Val	Leu	Ala	Pro 415	Gly
,,,	Pro	Pro	Gln	Ala 420	_		Pro	Pro	Ala 425		Lys	Pro	Thr	Gln 430	Ala	Gly
•	Glu	Gly	Thr 435		Ser	Glu	Ala	Leu 440	Leu	Gln	Leu	Gln	Phe 445		Asp	Glu
50	Asp	Leu 450		Ala	Leu	Leu	Gly 455		Ser	Thr	Asp	Pro 460	Ala	Val	Phe	Thr
	Asp 465		Ala	Ser	Val	Asp 470	Asn	Ser	Glu	Phe	Gln 475		Leu	Leu	Asn	Glr 480
55	_				485					490			Leu		495	
	70	~ 7	777	T 7 ~	Th~	7 ~~~	7	17-7	m1	~1	. או ~	~ n	7~~	Dro	Dro	λer

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505
                 500
     Pro Ala Pro Ala Pro Leu Gly Ala Pro Gly Leu Pro Asn Gly Leu Leu
                                 520
     Ser Gly Asp Glu Asp Phe Ser Ser Ile Ala Asp Met Asp Phe Ser Ala
5
     Leu Leu Ser Gln Ile Ser Ser Leu Asp Pro Pro Val Ala Thr Met Val
                         550
                                              555
     Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu
                     565
                                          570
10
     Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly
                 580
                                     585
     Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr
                                  600
     Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr
15
                             615
                                                  620
     Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His
                          630
                                             635
     Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr
                                         650
                     645
20
     Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys
                 660
                                     665
     Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp
                                  680
     Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr
25
     Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile
                          710
                                              715
     Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln
                     725
                                          730
     Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val
30
                                      745 ·
     Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys
                                 760
     Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr
35
                              775
     Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
                          790
               (2) INFORMATION FOR SEQ ID NO:142:
40
            (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 2394 base pairs
              (B) TYPE: nucleic acid
              (C) STRANDEDNESS: single
45
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: cDNA
            (ix) FEATURE:
50
               (A) NAME/KEY: Coding Sequence
               (B) LOCATION: 1...2391
               (D) OTHER INFORMATION:
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:
55
      ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG
                                                                               294
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	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu	·	
5		GAG Glu															96	
10		GGC Gly														_	144	
15		ACC Thr 50															192	
15		ACC Thr															240	
20		CAC His		_													288	
25		ACC Thr			Phe											_	336	
30		AAG Lys															384	
25	ATC	GAC Asp 130															.432	
35		TAC Tyr														AAC Asn 160	480	
40		ATC Ile															528	
45										Asn					Asp	GGC Gly	576	
50									Tyr					Ser		CTG Leu	624	
								Arg					Leu			TTC Phe	672	
55	GTG	ACC	GCC	GCC	GGG	ATC	ACT	CTC	GGC	ATG	GAC	GAG	CTG	TAC	: AAG	TCC	720	295

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	Val 225	Thr	Ala	Ala	Gly	Ile 230	Thr	Leu	Gly	Met	Asp 235	Glu	Leu	Tyr	Lys	Ser 240		
5				TCT Ser													768	
10				GCC Ala 260													816	
				CGG Arg													864	
15				ATC Ile													912	
20				AAG Lys													960	
25	TCC			ACC Thr													1008	
30				GAC Asp 340													1056	
				ATC Ile													1104	
35				CTG Leu									Gln				1152	
40				CAA			Ile										1200	
45				CGG Arg													1248	
50										Pro					Asp	AAT	1296	
				Asn					Lys					Asn		AAC Asn	1344	
55	TCT	GGC	AGC	TGC	CTC	GGT	. GGG	GAT	' GAG	ATC	TTC	CT	CTG	; TGI	GAC	: AAG	1392	296

									•			•					
	Ser	Gly 450	Ser	Cys	Leu	Gly	Gly 455	Asp	Glu	Ile	Phe	Leu 460	Leu	Cys	Asp	Lys	
5		CAG Gln															1440
10		CGA Arg															1488
15		TTC Phe															1536
15		GTC Val															1584
20		ATG Met 530															1632
25		GAG Glu															1680
30		AGT Ser															1728
35		GCT Ala															1776
33		CCC Pro															1824
40		CCC Pro 610															1872
45		GCC Ala															1920
50		GCT Ala														_	1968
55		GTC Val															2016
VJ	AAG	CCC	ACC	CAG	GCT	GGG	GAA	GGA	ACG	CTG	TCA	GAG	GCC	CTG	CTG	CAG	2064

	Lys	Pro	Thr 675	Gln	Ala	Gly	Glu	Gly 680	Thr	Leu	Ser	Glu	Ala 685	Leu	Leu	Gln		
5				GAT Asp													2112	
				GTG Val													2160	
				CTG Leu												GAG Glu	2208	
15				ATG Met 740													2256	
20	GCC Ala	CAG Gln	AGG Arg 755	Pro	CCC Pro	GAC Asp	CCA Pro	GCT Ala 760	Pro	GCT Ala	CCA Pro	CTG Leu	GGG Gly 765	GCC Ala	CCG Pro	GGG Gly	2304	
25	CTC Leu	CCC Pro 770	Asn	GGC	CTC Leu	CTT Leu	TCA Ser 775	Gly	GAT Asp	GAA Glu	GAC	TTC Phe 780	Ser	TCC	Ile	GCG Ala	2352	
30	GAC Asp 785	Met	GAC	TTC Phe	TCA Ser	GCC Ala 790	Leu	CTG Leu	AGT Ser	CAG Gln	ATC Ile 795	Ser	TCC Ser	TAA			2394	
			(2) IN	FORM	ATIO	n fo	R SE	Q II	NO:	143:						`	
35			(A) (B) (C)	EQUE LEN TYP STR	GTH: E: a ANDE	797 mino DNES	ami aci S: s	no a d ingl	cids							·		ż
40			(ii)	TOP MOLE RAGM	CULE	TYP	E: p	rote								•		
45	Met			SEQU								*		l Pro	o Il	e Leu		
	1 Val	l Glu	ı Lev	ı Asp 20	5 Gl ₃	/ Asp	val	l Ası	n Gly 25	10 y His	s Ly:	s Phe	e Se	r Va. 30		r Gly		
50			35	ı Gly				40					45			e Ile		
	-	50					55					60				r Thr t Lys		
55	65		_			70					75					80 n Glu		29

															^-	
			_		85	_	_	_		90		*	mh sa		95	01. ,
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	G1y 105	Asn	ıyr	гÀв	Thr	110	Ala	GIU
5	Val	Lys	Phe 115	Glu	Gly	Asp	Thr	Leu 120	Val	Asn	Arg	Ile	Glu 125	Leu	Lys	Gly
	Ile	Asp		Lys	Glu	Asp	Gly 135		Ile	Leu	Gly	His 140	Lys	Leu	Glu	Tyr
• •	λαη	130 Tyr	Δan	Ser	His	Asn		Tvr	Ile	Met	Ala		Lys	Gln	Lys	Asn
	145	171				150		-1-			155	•	•		•	160
10 .	Gly	Ile	ГÀв	.Val	Asn 165	Phe	Lys	Ile	Arg	His 170	Asn	Ile	Glu	Asp	Gly 175	Ser
•	Val	Gln	Leu	Ala 180		His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly
15	Pro	Val	Leu 195		Pro	Asp	Asn	His 200	Tyr	Leu	Ser	Thr	Gln 205	Ser	Ala	Leu
10	Ser	Lys 210		Pro	Asn	Glu	Lys 215	Arg	Asp	His	Met	Val 220	Leu	Leu	Glu	Phe
	Val 225	Thr	Ala	Ala	Gly	Ile 230		Leu	Gly	Met	Asp 235	Glu	Leu	Tyr	Lys	Ser 240
20	Gly	Leu	Arg	Ser	Arg 245		Met	Asp	Glu	Leu 250	Phe	Pro	Leu	Ile	Phe 255	Pro
	Ala	Glu	Pro	Ala 260		Ala	Ser	Gly	Pro 265	Tyr	Val	Glu	Ile	Ile 270	Glu	Gln
25	Pro	Lys	Gln 275		Gly	Met	Arg	Phe 280		Tyr	Lys	Cys	Glu 285	Gly	Arg	Ser
25	Ala	Gly 290		Ile	Pro	Gly	Glu 295	Arg		Thr	Asp	Thr	Thr	Lys	Thr	His
	Pro 305	Thr	Ile	Lys	Ile	Asn 310	Gly		Thr	Gly	Pro 315	Gly	Thr	Val	Arg	Ile 320
30	Ser	Leu	Val	Thr	Lys 325			Pro	His	Arg		His	Pro	His	Glu 335	Leu
	Val	Gly	Lys	Asp	Суѕ	Arg	Asp	Gly	Phe 345		Glu	Ala	Glų	Leu 350		Pro
35	Asp	Arg	Cys 355	Ile		Ser	Phe	Gln 360		Leu	Gly	Ile	Gln 365		Val	Lys
00	Lys	Arg	Asp		Glu	Gln	Ala 375		Ser	Gln	Arg	Ile 380		Thr	Asn	Asn
	Asn			Gln	Val			Glu	Glu	Gln			Asp	Tyr	Asp	Leu
	385			_	_	390				m)	395		. 70-	Dro	Cor	400
40					405					410)				415	
				420)				425	i				430)	Asn
45			435	;				440)				445	5		Asn
		450)				455	5				460)			Lys
	Va] 465		Lys	Glu	Asp	11∈ 470		ı Val	l Tyı	. Phe	e Thi 47!		/ Pro	Gl3	/ Trp	Glu 480
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CLAIMS

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- 1. A method for extracting quantitative information relating to an influence on a cellular response, the method comprising recording variation, caused by the influence on a mechanically intact living cell or mechanically intact living cells, in spatially distributed light emitted from a luminophore, the luminophore being present in the cell or cells and being capable of being redistributed in a manner which is related with the degree of the influence, and/or of being modulated by a component which is capable of being redistributed in a manner which is related to the degree of the influence, the association resulting in a modulation of the luminescence characteristics of the luminophore, and processing the recorded variation in the spatially distributed light to provide quantitative information correlating the spatial distribution to the degree of the influence on the cellular response.
- 2. A method according to claim 1, as used for extracting quantitative information relating to an influence on an intracellular pathway involving redistribution of at least one component associated with the pathway, or part thereof, the method comprising recording the result of the influence on mechanically intact living cell or cells, as manifested in spatially distributed light emitted from a luminophore which is present in the cell or cells and which is capable of being redistributed, by modulation of the pathway, in a manner which is related to the redistribution of the at least one component of the intracellular pathway, processing the recorded result to provide quantitative information about the spatially distributed light and correlating the quantitative information to the degree of the influence on the intracellular pathway.
- 3. A method according to claim 1 or 2, wherein the quantitative information which is indicative of the degree of the cellular response to the influence or the result of the influence on the intracellular pathway is extracted from the recording or recordings according to a predetermined calibration based on responses or results, recorded in the same manner, to known degrees of a relevant specific influence.
- 4. A method according to any of the preceding claims, wherein the influence is contact between the mechanically intact living cell or the group of mechanically intact living cells with a

chemical substance and/or incubation of the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance.

- 5. A method according to claim 4 wherein the substance is a substance whose effect on an intracellular pathway is to be determined.
- 6. A method according to any of the preceding claims, wherein the recording is made at a single point in time after the application of the influence.
- 7. A method according to any of claims 1-5, wherein the recording is made at two points in time, one point being before, and the other point being after the application of the influence.
 - 8. A method according to any of claims 1-5, wherein the recording is performed at a series of points in time, in which the application of the influence occurs at some time after the first time point in the series of recordings, the recording being performed, e.g., with a predetermined time spacing of from 0.1 seconds to 1 hour, preferably from 1 to 60 seconds, more preferably from 1 to 30 seconds, in particular from 1 to 10 seconds, over a time span of from 1 second to 12 hours, such as from 10 seconds to 12 hours, e.g., from 10 seconds to one hour, such as from 60 seconds to 30 minutes or 20 minutes.

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- 9. A method according to any of claims 1-7, wherein the cell or cells is/are fixed at a point in time after the application of the influence at which the response has been predetermined to be significant, and the recording is made at an arbitrary later time.
- 10. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence.

- 11. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of associating with a component which is capable of being redistributed in manner which is physiologically relevant to the degree of the influence.
- 12. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed in a manner which is experimentally determined to be correlated to the degree of the influence.
- 13. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed, by modulation of the intracellular pathway, in substantially the same manner as the at least one component of the intracellular pathway.
 - 14. A method according to any of claims 1-13, wherein the luminophore is a luminophore which is capable of being quenched upon spatial association with a component which is redistributed by modulation of the pathway, the quenching being measured as a decrease in the intensity of the luminescence.
- 15. A method according to any of claims 1-13, wherein the variation or result with respect to the spatially distributed light emitted by the luminophore is detected by a change in the resonance energy transfer between the luminophore and another luminescent entity capable of delivering energy to the luminophore, each of which has been selected or engineered to become part of, bound to or associated with particular components of the intracellular pathway, and one of which undergoes redistribution in response to the influence, thereby changing the amount of resonance energy transfer, the change in the resonance energy transfer being measured as a change in the intensity of emission from the luminophore.
 - 16. A method according to claim 15, wherein the change in the intensity of the emission from the luminophore is sensed by a single channel photodetector which responds only to the average intensity of the luminophore in a non-spatially resolved fashion

17. A method according to any of claims 1-16, wherein the property of the light being recorded is intensity, fluorescence lifetime, polarization, wavelength shift, or other property which is modulated as a result of the underlying cellular response.

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- 18. A method according to any of claims 1-15 or 17, wherein the recording of the spatially distributed light is performed using a recording system which records the spatial distribution of a recordable property of the light in the form of an ordered array of values.
- 19. A method according to claim 18, wherein the recording of the spatial distribution of the recordable property of the light is performed using a charge transfer device such as a CCD array or a vacuum tube device such as a vidicon tube.
- 20. A method according to any of the preceding claims, wherein the light to be measured
 passes through a filter which selects the desired component of the light to be measured and rejects other components.
 - 21. A method according to any of the preceding claims, wherein the recording of the spatial distribution of the recordable property of light is performed by fluorescence microscopy.

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22. A method according to any of the preceding claims, wherein the recording of the variation or result with respect to light emitted from the luminophore is performed by recording the spatially distributed light as one or more digital images, and the processing of the recorded variation to reduce it to one or more numbers representative of the degree of redistribution comprises a digital image processing procedure or combination of digital image processing procedures.

23. A method according to any of claims 2-22, wherein the intracellular pathway is an intracellular signalling pathway.

- 24. A method according to any of the preceding claims, wherein the luminophore is a fluorophore.
- 25. A method according to any of the preceding claims wherein the luminophore is a polypeptide encoded by and expressed from a nucleotide sequence harboured in the cell or cells.
- 26. A method according to any of the preceding claims, wherein the luminophore is a hybrid polypeptide comprising a fusion of at least a portion of each of two polypeptides one of which comprises a luminescent polypeptide and the other one of which comprises a biologically active polypeptide, as defined herein.
- 27. A method according to claim 26, wherein the luminescent polypeptide is a GFP as defined herein.
 - 28. A method according to claim 27 wherein the GFP is selected from the group consisting of green fluorescent proteins having the F64L mutation as defined herein.
- 29. A method according to claim 28 wherein the GFP is a GFP variant selected from the group consisting of F64L-GFP, F64L-Y66H-GFP, F64L-S65T-GFP, and EGFP.
 - 30. A method according to any of the previous claims for detecting intracellular translocation of a biologically active polypeptide affecting intracellular processes upon activation, the method comprising
 - a) culturing one or more cells containing a nucleotide sequence coding for a hybrid polypeptide comprising a GFP which is N- or C-terminally tagged, optionally through a linker, to a biologically active polypeptide under conditions permitting expression of the nucleotide sequence,

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- b) modulating the activity of the biologically active polypeptide by incubating the cell or cells with a substance having biological activity and
- c) measuring the fluorescence produced by the incubated cell or cells and determining the result or variation with respect to the fluorescence, such result or variation being indicative of the translocation of a biologically active polypeptide in said cell.
- 31. A method according to claim 30, wherein the nucleotide sequence is a DNA sequence.
- 32. A method according to claim 30 or 31, wherein the modulation is an activation.
- 33. A method according to claim 30 or 31, wherein the modulation is a deactivation.
- 34. A method according to any of claims 30-33 wherein the fluorescence of the cell or cells is measured prior to the modulation, and the result or variation determined in step (c) is a change in fluorescence compared to the fluorescence measured prior to the modulation.
- 35. A method according to any of claims 30-34, wherein the intracellular processes are intracellular signalling pathways.
- 36. A method according to claim 34, wherein the change in fluorescence measured in step(c) comprises determining a change in the spatial distribution of the fluorescence.
 - 37. A method according to any of the preceding claims wherein the mechanically intact living cell or cells is/are a mammalian cell/mammalian cells which, during the time peroid over which the influence is observed, is/are incubated at a temperature of 30°C or above, preferably at a temperature of from 32°C to 39°C, more preferably at a temperature of from 35°C to 38°C, and most preferably at a temperature of about 37°C.

thereof.

- 38. A method according to any of the preceding claims, wherein the at least one mechanically intact living cell is part of a matrix of identical or non-identical cells.
- 39. A method according to any of claims 1-36 and 38, wherein the cell or cells is/are selected from the group consisting of fungal cells, such as a yeast cell; invertebrate cells including insect cells; and vertebrate cells, such as mammalian cells.
- 40. A nucleic acid construct coding for a fusion polypeptide comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and
 10 a GFP, with the proviso that the construct is not a construct coding for a fusion polypeptide in which the biologically active polypeptide is selected from the group consisting of PKC-alpha, PKC-gamma, and PKC-epsilon.
- 41. A nucleic acid construct coding for a fusion polypeptide comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and an F64L mutant of GFP.
 - 42. A nucleic acid construct according to claim 40 or 41, wherein the biologically active polypeptide is a protein kinase or a phosphatase.
 - 43. A nucleic acid construct according to any of claims 40-42 wherein the GFP is N- or C-terminally tagged, optionally via a peptide linker, to the biologically active polypeptide or part
- 44. A nucleic acid construct according to any of claims 40, 41 and 43, wherein the biologically active polypeptide is a transcription factor or a part thereof which changes cellular localisation upon activation.

- 45. A nucleic acid construct according to any of claims 40, 41 and 43, wherein the biologically active polypeptide is a protein, or a part thereof, which is associated with the cytoskeletal network and which changes cellular localisation upon activation.
- 46. A nucleic acid construct according to any of claims 40-43, wherein the biologically active polypeptide is a protein kinase or a part thereof which changes cellular localisation upon activation.
- 47. A nucleic acid construct according to claim 46, wherein the protein kinase is a serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
 - 48. A nucleic acid construct according to claim 46, wherein the protein kinase is a tyrosine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
 - 49. A nucleic acid construct according to claim 46, wherein the protein kinase is a phospholipid-dependent serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
- 50. A nucleic acid construct according to claim 46, wherein the protein kinase is a cAMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 51. A nucleic acid construct according to claim 50 which codes for a PKAc-F64L-S65T-GFP fusion.
 - 52. A nucleic acid construct according to claim 46, wherein the protein kinase is a cGMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.

53. A nucleic acid construct according to claim 46, wherein the protein kinase is a calmodulin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

- 54. A nucleic acid construct according to claim 46, wherein the protein kinase is a mitogenactivated serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 55. A nucleic acid construct according to claim 54, which codes for an ERK1-F64L-S65T-GFP fusion.
 - 56. A nucleic acid construct according to claim 54, which codes for an EGFP-ERK1 fusion.
- 57. A nucleic acid construct according to claim 46, wherein the protein kinase is a cyclindependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 58. A nucleic acid construct according to claim 42 or 43, wherein the biologically active polypeptide is a protein phosphatase or a part thereof capable of changing cellular localisation upon activation.
 - 59. A nucleic acid construct according to any of claims 40-58 which is a DNA construct.
- 60. A nucleic acid construct according to any of claims 40-59 wherein the gene encoding GFP is derived from Aequorea victoria.
 - 61. A nucleic acid construct according to claim 60 in which the gene encoding GFP is the gene encoding EGFP as defined herein.

62. A nucleic acid construct according to claim 60 in which the gene encoding a GFP is a gene encoding a GFP variant selected from F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP.

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- 63. A DNA construct according to claim 59 and 61 or, where applicable, 62, which is a construct as identified by any of the DNA sequences shown in SEQ ID NO: 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, and 142, or is a variant thereof capable of encoding the same fusion polypeptide or a fusion polypeptide which is biologically equivalent thereto, as defined herein.
- 64. A cell containing a nucleic acid construct according to any of claims 40-63 and capable of expressing the sequence encoded by the construct.

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- 65. A cell according to claim 64, which is a eukaryotic cell.
- 66. A cell according to claim 64, which is selected from the group consisting of fungal cells, such as yeast cells; invertebrate cells, including insect cells, and vertebrate cells, such as mammalian cells.
- 67. A cell according to claim 66, which is a mammalian cell.
- 68. An organism carrying in at least one of its component cells a nucleic acid sequence as contained in the constructs according to any of claims 40-59, said cell being capable of expressing said nucleic acid sequence.
 - 69. An organism according to claim 68 which is selected from the group consisting of unicellular and multicellular organisms, such as a mammal.

- 70. A fluorescent probe comprising a GFP which is N- or C-terminally tagged, optionally via a peptide linker, to a biologically active polypeptide or a part or a subunit thereof which is a component of a intracellular signalling pathway as defined herein, the probe being a probe which is encoded by the nucleic acid construct according to any of claims 40-59.
- 71. A method according to any of claims 1-39, wherein the luminophore is a fusion polypeptide as encoded by the nucleic acid construct according to any of claims 40-63.
- 72. A method according to any of claims 1-39 or 71 in which the method of the invention is used in a screening program as defined herein.
 - 73. An apparatus for measuring the distribution of fluorescence in at least one cell, and thereby any change in the distribution of fluorescence in at least one cell, which includes the following component parts: (a) a light source, (b) a means for selecting the wavelength(s) of light from the source which will excite the fluorescence of the protein, (c) a means for rapidly blocking or pass ing the excitation light into the rest of the system, (d) a series of optical elements for conveying the excitation light to the specimen, collecting the emitted fluorescence in a spatially resolved fashion, and forming an image from this fluorescence, (e) a bench or stand which holds the container of the cells being measured in a predetermined geometry with respect to the series of optical elements, (f) a detector to record the spatially resolved fluorescence in the form of an image, (g) a computer or electronic system and associated software to acquire and store the recorded images, and to compute the degree of redistribution from the recorded images.

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- 74. An apparatus according to claim 73 in which some or all of the system is automated.
- 75. An apparatus according to claim 73 in which components d and e comprise a fluorescence microscope.

- 76. An apparatus according to claim 73 in which component f is a CCD camera.
- 77. An apparatus according to claim 73 in which the image is formed and recorded by an optical scanning system.

- 78. An apparatus according to claim 73 in which a liquid addition system is used to add a known or unknown compound to any or all of the cells in the cell holder at a time determined in advance.
- 79. An apparatus according to claim 78 in which the liquid addition system is under the control of the computer or electronic system.
 - 80. A method according to any of claims 1-79 wherein the method is a screening program for the identification of a biologically active substance as defined herein that directly or indirectly affects an intracellular signalling pathway and is potentially useful as a medicament, wherein the result of the individual measurement of each substance being screened which indicates its potential biological activity is based on measurement of the redistribution of spatially resolved luminescence in living cells and which undergoes a change in distribution upon activation of an intracellular signalling pathway.

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- 81 A method according to any of claims 1-79 wherein the method is a screening program for the identification of a biologically toxic substance as defined herein that exerts its toxic effect by interfering with an intracellular signalling pathway, wherein the result of the individual measurement of each substance being screened which indicates its potential biologically toxic activity is based on measurement of the redistribution of said fluorescent probe in living cells and which undergoes a change in distribution upon activation of an intracellular signalling pathway.
- 82. A method according to any of claims 1-80 wherein a fluorescent probe is used in back-30 tracking of signal transduction pathways as defined herein.

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- 83. A method of treating a condition or disease related to the intracellular function of a protein kinase comprising administering to a patient suffering from said condition or disease an effective amount of a compound which has been discovered by any method according to the invention.
- 84. A compound that modulates a component of an intracellular pathway as defined herein, as determined by a method according to the method of the invention.
- 85. A medical composition comprising a therapeutic amount of a compound identified according the method of the invention.
 - 86. A method of selectively treating a patient suffering from an ailment which responds to medical treatment comprising obtaining a primary cell or cells from said patient, transfecting the cell or cells with at least one DNA sequence encoding a fluorescent probe according to the invention, culturing the cell or cells under conditions permitting the expression of said probes and exposing it to an array of medicaments suspected of being capable of alleviating said ailment, then comparing changes in fluorescence patterns or redistribution patterns of the fluorescent probes in the intact living cell or cells to detect the cellular response to the specific medicaments (obtaining a cellular action profile), then selecting a medicament(s) based on desired activity and acceptable level of side effects and administering an effective amount of said medicament(s) to said patient.
- 87. A method according to any of claims 1-80 of identifying a drug target among the group of biologically active polypeptides which are components of intracellular signalling pathways.

Fig 1

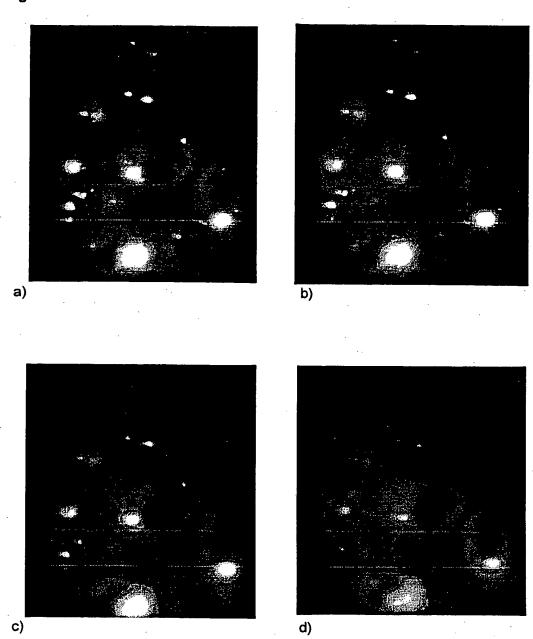
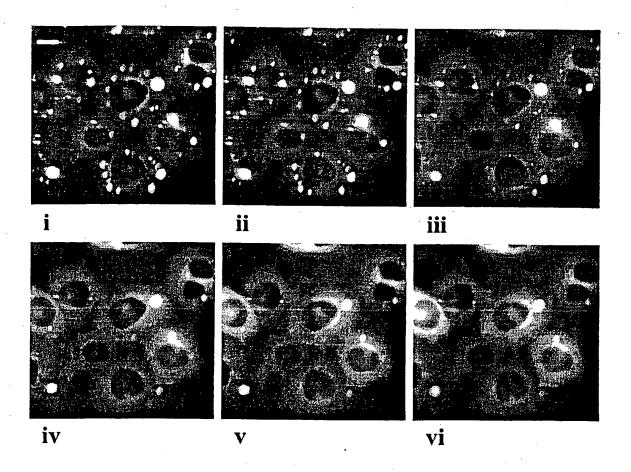
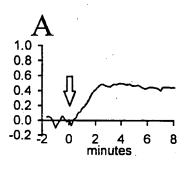


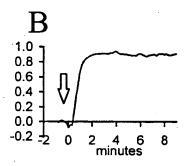
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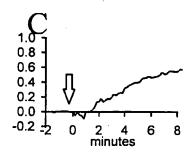


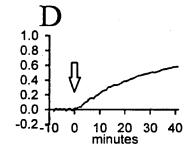
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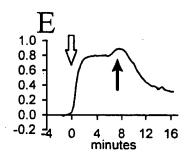
Fig 3

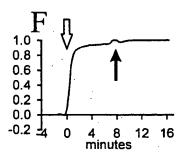


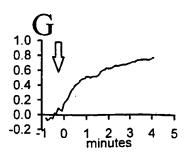












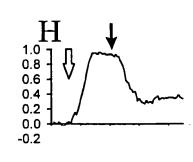
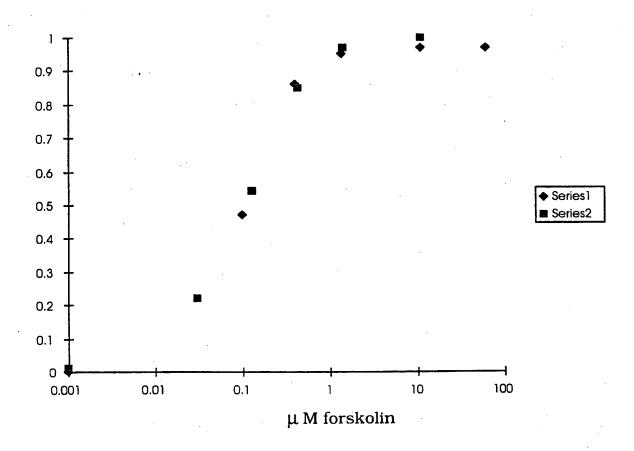


Fig 4



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Fig 5

[forskolin]µM	$t_{1/2max}/s$	t _{max} /s
1	115±21	310±31
10	69±14	224±47
50	47±10	125±28

Fig 6

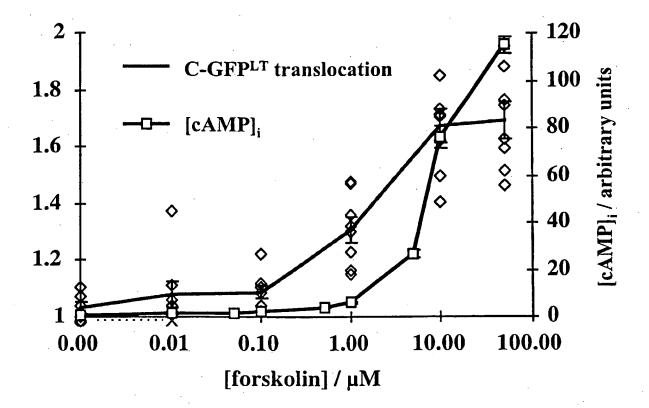
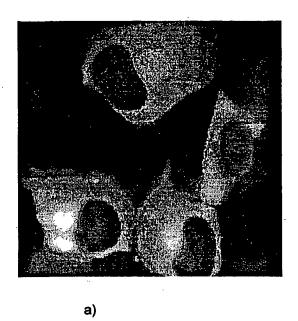
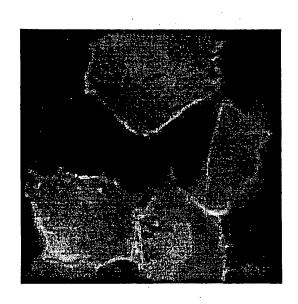
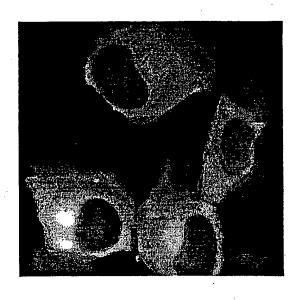


Fig 7



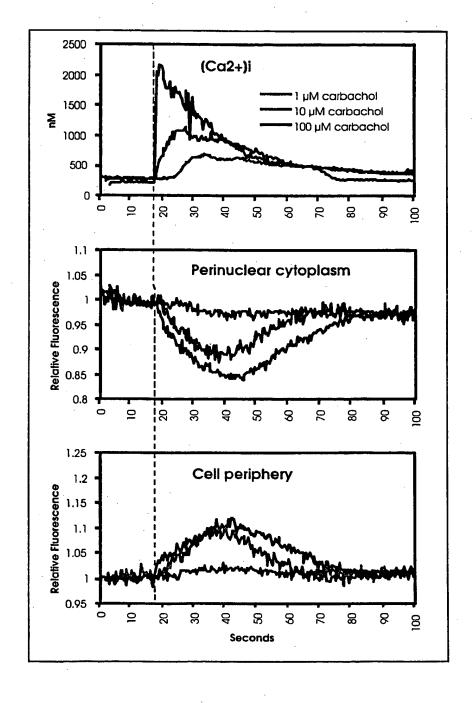




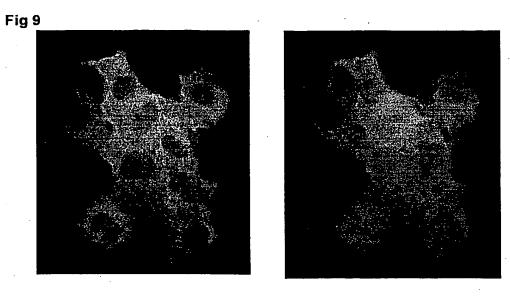


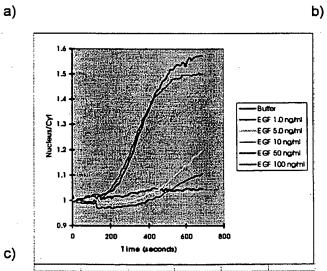
c)

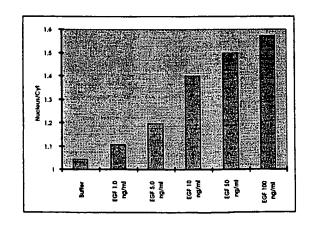
Fig 8









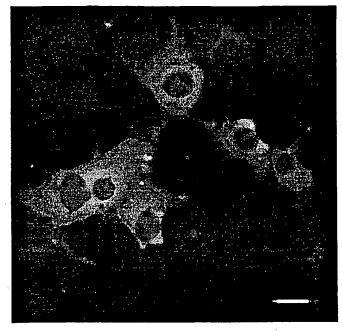


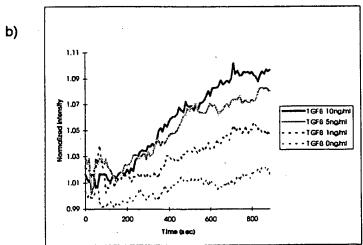
d)

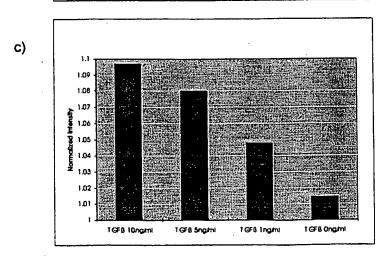
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Fig 10



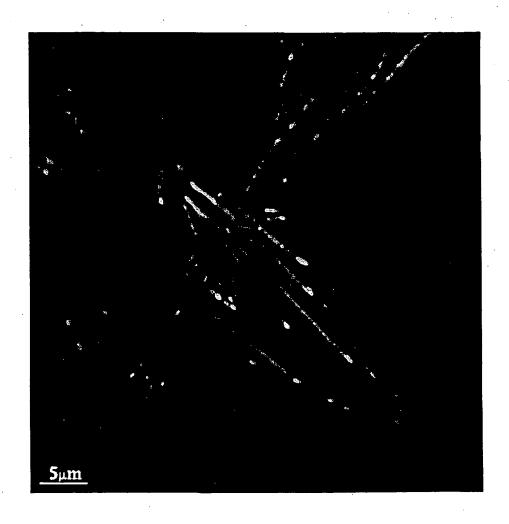






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Fig 11

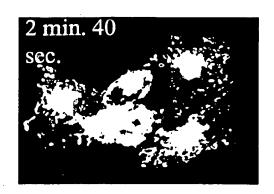


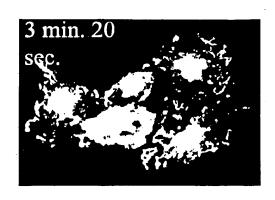
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Fig. 12













PCT

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6:

G01N 33/50, C12Q 1/48, 1/25

A3

(11) International Publication Number: WO 98/45704

(43) International Publication Date: 15 October 1998 (15.10.98)

(21) International Application Number:

PCT/DK98/00145

(22) International Filing Date:

7 April 1998 (07.04.98)

(30) Priority Data:

0392/97

7 April 1997 (07.04.97)

DK

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, IP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:

22 April 1999 (22.04.99)

(54) Title: A METHOD FOR EXTRACTING QUANTITATIVE INFORMATION RELATING TO AN INFLUENCE ON A CELLULAR RESPONSE

(57) Abstract

Cells are genetically modified to expresss a luminophore, e.g., a modified (F64L, S65T, Y66H) Green Fluorescent Protein (GFP, EGFP) coupled to a component of an intracellular signalling pathway such as a transcription factor, a cGMP- or cAMP-dependent protein kinase, a cyclin-, calmodulin- or phospholipid-dependent or mitogen-activated serine/threonin protein kinase, a tyrosine protein kinase, or a protein phosphatase (e.g. PKA, PKC, Erk, Smad, VASP, actin, p38, Jnk1, PKG, IkappaB, CDK2, Grk5, Zap70, p85, protein-tyrosine phosphatase 1C, Stat5, NFAT, NFkappaB, RhoA, PKB). An influence modulates the intracellular signalling pathway in such a way that the luminophore is being redistributed or translocated with the component in living cells in a manner experimentally determined to be correlated to the degree of the influence. Measurement of redistribution is performed by recording of light intensity, fluorescence lifetime, polarization, wavelength shift, resonance energy transfer, or other properties by an apparatus consisting of e.g. a fluorescence microscope and a CCD camera. Data stored as digital images are processed to numbers representing the degree of redistribution. The method can be used as a screening program for identifying a compound that modulates a component and is capable of treating a disease related to the function of the component.

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Int. itional Application No

PCT/DK 98/00145 CLASSIFICATION OF SUBJECT MATTER PC 6 G01N33/50 C120 C12Q1/48C1201/25According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) GO1N C120 C12N C07K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. Category 5 WO 97 11094 A (NOVONORDISK AS ;THASTRUP 1-27X 30 - 40, OLE (DK); TULLIN SOEREN (DK); POULSEN LAR) 44-60, 27 March 1997 64-82,88 see the whole document 28,29, γ see claims 41,61-63 X WO 91 01305 A (UNIV WALES MEDICINE) 1-27, 30 - 40, 7 February 1991 42-60, 64-84, 87,88 see page 4, line 15 - line 20 Υ 28,29, see claims 41,61-63 see examples 1-10 Patent family members are listed in annex. Further documents are listed in the continuation of box C. Special categories of cited documents: T: later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international X document of particular relevance; the claimed invention filing date cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another document of particular relevance; the claimed invention citation or other special reason (as specified) cannot be considered to Involve an inventive step when the document is combined with one or more other such docu-"O" document referring to an oral disclosure, use, exhibition or ments such combination being obvious to a person skilled other means document published prior to the international filing date but later than the priority date claimed n ine art Date of the actual completion of the international search Cate of mailing of the international search report 25. 02. 1999 19 January 1999 Authorized officer Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL · 2280 HV Rijswijk

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C.(Continu	ation). DOCUMENTS CONSIDERED TO BE RELEVANT	
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ational application No. PCT/DK 98/00145

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 83-84 and claim 87 relate to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition (Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy). 2. X Claims Nos.: 85,86 because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically: See FURTHER INFORMATION sheet PCT/ISA/210
330 1 32 2 3 3 3 3 3
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
see additional sheet
1. X As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest The additional search fees were accompanied by the applicant's protest.
No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 85,86

The subject-matter (compounds per se) is solely characterised in claims 85 and 86 by the result to be achieved, no support of a technical character is derivable from the description for the technical formulation of the subject of the search, accordingly no scope of a search could be defined and a meaningfull search is hence not possible.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 47, 49, 53-57

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being serine/threonine protein kinases

2. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 48

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to tyrosine kinases

3. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 50, 51

MMethods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to cAMP dependent protein kinases.

4. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 52

MMethods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being cGMP dependent protein kinases

5. Claims: Partially: 1-43, 59-82 and 88; Entirely: 58

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being protein phosphatases

6. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 44

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to transcription factors

7. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 45

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to proteins associated with the cytoskeletal network

Information on patent family members

PCT/DK 98/00145

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